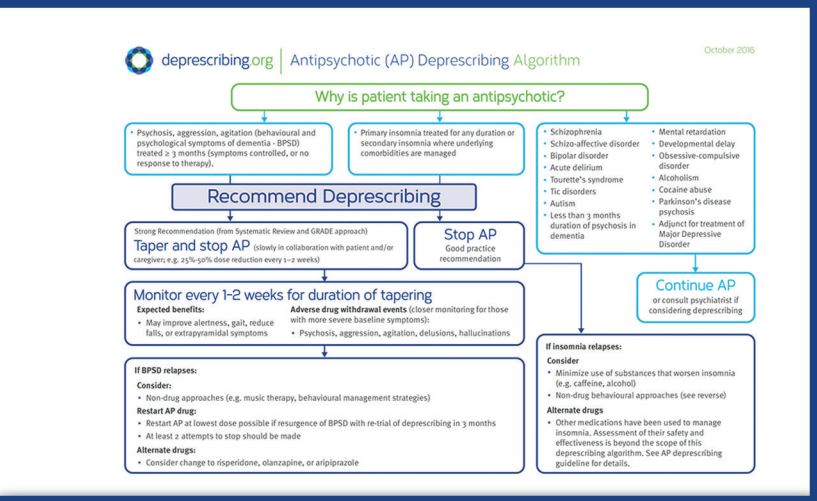
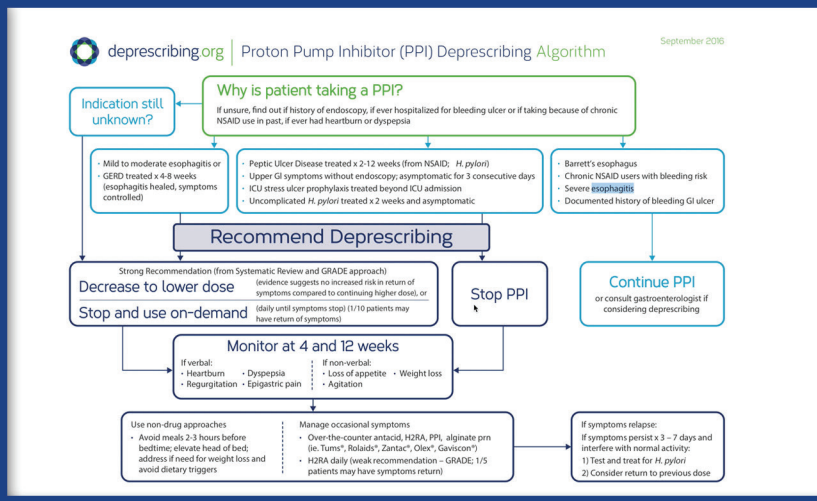
March 2018

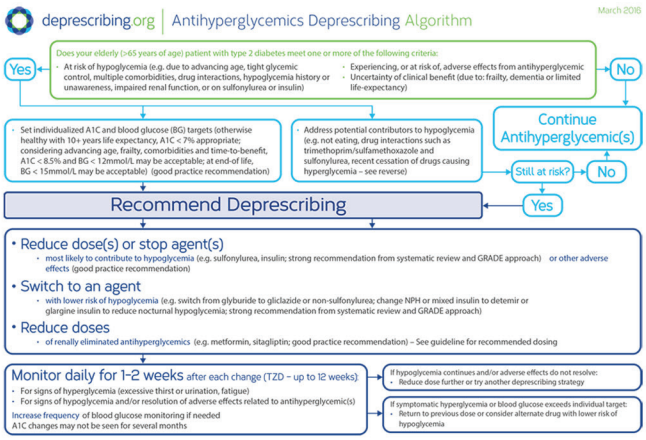
Developing an Evidence-based Deprescribing Guideline:

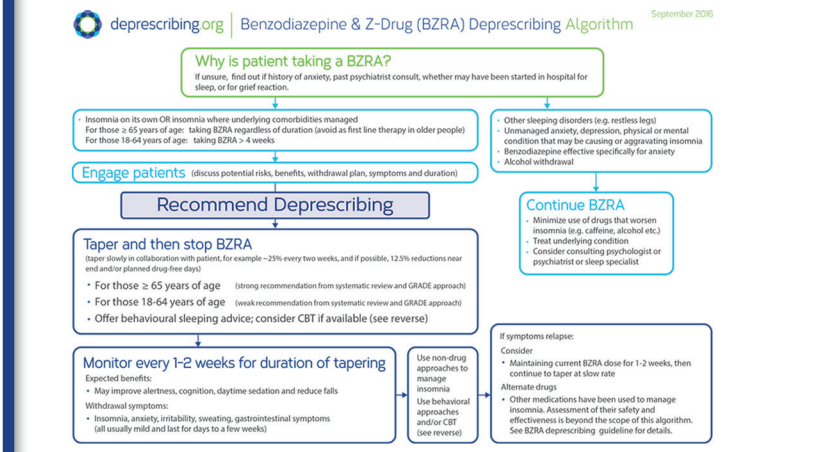
INSTRUCTION MANUAL

For Guideline Coordinators









Deprescribing guideline development supported by:

Production of this manual supported by:

Authors

Wade Thompson, Lisa Pizzola, Matthew Hogel, Cody Black, Barbara Farrell

To cite this manual

Thompson W, Pizzola L, Hogel M, Black CD, Farrell B. Developing an evidence-based deprescribing guideline: instruction manual for guideline coordinators (working document). 2018. https://deprescribing.org/resources/deprescribing-guidelines-algorithms/ .

Agreement

In using this deprescribing guideline instruction manual, the user agrees to register their guideline with the deprescribing@bruyere.org team and to invite a member to act as one of the authors or reviewers to ensure consistency with the rigorous standards developed by the team.

Copyright

Acknowledgments

The Deprescribing Guidelines Program aims to rigorously develop evidence-based guidelines to help clinicians deprescribe medications that are no longer needed, or where harm may outweigh benefit. The program has been supported by the Ontario Government through the Ontario Pharmacy Evidence Network and by the Canadian Institutes of Health Research. The Program is located in the Bruyère Research Institute in Ottawa, Canada.

This manual is a working document created through the efforts of the Deprescribing Guideline Coordinators, with leadership from the Deprescribing Guidelines Methods Committee members: Kevin Pottie, Carlos Rojas-Fernandez, Barbara Farrell. Deprescribing project co-investigators, James Conklin, Lalitha Raman-Wilms and Lisa McCarthy, also provided input, along with staff members Michael Elten, David deLaunay and Hannah Irving.

Each Guideline Development Team (GDT) contributed time and expertise:
Proton pump inhibitor deprescribing GDT members: Barbara Farrell, Kevin Pottie, Kate Walsh, Vivian Welch, Paul Moayyedi.

Benzodiazepine receptor agonist deprescribing GDT members: Kevin Pottie, Simon Davies, Jean Grenier, Cheryl Sadowski, Vivian Welch, Anne Holbrook, Cynthia Boyd, Robert Swenson, Barbara Farrell.

Antipsychotic deprescribing GDT members: Lise Bjerre, Andrew Wiens, Genevieve Lemay, Lalitha Raman-Wilms, Lisa McCarthy, Lyla Graham, Samir Sinha, Vivian Welch, Barbara Farrell.

Antihyperglycemic deprescribing GDT members: Barbara Farrell, Lisa McCarthy, Carlos Rojas-Fernandez, Heather Lochnan, Salima Shamji, Ross Upshur, Manon Bouchard, Vivian Wlech.

We also acknowledge the many students and residents who have contributed to each guideline and to the processes outlined in this manual: Taline Boghossian, Joy Rashid, Sonia Hussain, Andy Ma, Elli Polemiti, Yan Li.

Funding disclaimer

The views expressed in this manuscript are those of the authors and do not necessarily reflect those of the funders.

Table of Contents

Introduction

Purpose

The purpose of this manual is to provide step-by-step instructions for developing a medication class specific evidence-based deprescribing guideline. This manual is for individuals coordinating the development of such guidelines, as well as those who require an estimate of the workload, activities and time involved in such development to establish accurate timelines and budgets.

Background

Deprescribing is the planned and supervised process of tapering or stopping of medication that may no longer be providing benefit, or that may be causing harm. The goal of deprescribing is to reduce medication burden and harm, while maintaining or improving quality of life.

An evidence-based deprescribing guideline uses syntheses of evidence for deprescribing, as well as considerations such as benefit of ongoing use of the target medication, patient values and preferences, knowledge of medication harms and economic considerations, to make recommendations for when and how to consider tapering or stopping medications.

Instructions are provided for guideline development teams (GDT) to grade recommendations for quality or certainty of evidence and strength using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation).

TIP

Refer to most recent GRADE approach regarding whether to use "quality" or "certainty" of evidence. The deprescribing guidelines used "quality" but GRADE has been working on changing to an assessment of "certainty."

Outline

This manual is organized into five main sections:

Section 1 – Preparing to develop a deprescribing guideline

Section 2 – Establishing a GDT and preparing for its tasks

Section 3 – Drafting the guideline

Section 4 – Conducting clinical and stakeholder reviews

Section 5 – Facilitating knowledge mobilization

Examples are drawn from the author teams' experiences in developing the first four deprescribing guidelines (proton pump inhibitors [PPIs], benzodiazepine receptor agonists [BZRAs], antipsychotics and antihyperglycemics).

Section 1: Preparing to develop a deprescribing guideline

In this section a number of important readings are recommended to prepare GDT leads and coordinators to complete the work of developing an evidence-based deprescribing guideline. A sample budget is also included to indicate costs associated with developing an evidence-based deprescribing guideline following the methods outlined in this manual.

Main Steps:

1.1 Prior viewing and reading

1.2 Draft a budget

1.1 Prior viewing and reading

To prepare yourself to lead and coordinate a GDT, ensure you are familiar with the following resources:

Introductory video

Developing Deprescribing Guidelines to Help Manage Polypharmacy and Improve Outcomes for Patients, with Dr Barbara Farrell. Available: www.youtube.com/watch?v=yfINQr4RptY

Guideline development methods[1,2]

Schünemann HJ, Wiercioch W, Etxeandia I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *CMAJ.* 2014;186(3):E123-42. Available: www.cmaj.ca/content/early/2013/12/16/cmaj.131237

Farrell B, Pottie K, Rojas-Fernandez C, et al. Methodology for developing deprescribing guidelines: using evidence and GRADE to guide recommendations for deprescribing. PLOS ONE 2016; available: DOI: http://dx.doi.org/10.1371/journal.pone.0161248

Systematic review methods[3]

Higgins JPT, Green S, eds. *Cochrane Handbook of Systematic Reviews of Intervention.* Version 5.1.0 (Updated March 2011). The Cochrane Collaboration, 2011. Available: http://handbook-5-1.cochrane.org/ (accessed Feb. 19,2018).

TIP

We recommend familiarizing yourself with Cochrane systematic review methods. Ideally, you should include a relevant Cochrane committee member on your GDT to expedite review.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[4]

Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339(1).

Online resources: www.prisma-statement.org/

***The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods*[5]**

Guyatt G, Oxman A, Akl E, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*. 2011;64(4):382-94. Online resources: http://gradeworkinggroup.org/

1.2 Draft a budget

Critical budget items for efficient development of a deprescribing guideline are:

- Coordinator salary
- Medical librarian consultation
- Support staff (research assistants, students)
- Consumables
- GDT meetings (x2)
- Knowledge translation: open access fees, poster printing, etc.

A sample budget with justifications is outlined below. Coordinator staff may be involved in developing budgets for funding proposals, or may be hired after these budgets have been established. Funds are in 2018 Canadian dollars.

Sample budget:

Personnel Services	FTE/ Number of Days/ Hours	Cost	Details
Research Associate/coordinator	0.5 FTE for 8 months(1300 hours)	$57,018	$34/hour + 29% vacation & benefits For coordination of literature syntheses (e.g., Title and abstract review for systematic reviews, scoping reviews) and guideline development activities (e.g., coordinating meetings, drafting guideline and decision support tool content, facilitating clinical and stakeholder review and subsequent revisions, preparing dissemination activities such as posters and publication)
Trainee (e.g., full-time co-op student or MSc student stipend)	4 months (600 hours)	$10,800	$18/hour for co-op student to contribute to various aspects of the syntheses, including acting as second rater for systematic review, and other deprescribing guideline development activities.
Consumables			
Supplies and expenses		$3408	Includes cost of printing/copying ($400), long-distance calls given national scope of team ($500), webconferencing for GDT meetings ($500), purchasing articles identified in systematic review ($800), Endnote licence ($644 for 2 licences), and six-month subscription to Adobe InDesign ($624) for decision support tool creation.
Catering for two face-to-face team meetings		$1200	Catering

Cochrane Systematic Review Training for two team members, estimated from Vancouver 2015 workshop		$4480	Includes registration fees ($600), travel ($1600), accommodation ($1800) and food ($480).
Supplies and Services			
Library Services	14 hours – scoping review 70 hours – systematic review (84 hours total)	$8543	$90/hour + HST. To execute systematic and scoping review searches, remove duplicate results
Statistical Services	16 hours	$904	$50/hour + HST. To conduct the meta-analysis.
Methodological Services	17 hours	$961	$50/hour + HST. Strategy development (1hour), defining outcomes (1 hour), eligibility & extraction form development (2 hours), article review (5 hours),
Travel			
Transportation		$15,960	For two GDT face-to-face meetings: investigator travel for seven people; includes airfare ($580/person), taxi and airport parking ($80/person), meal per diem ($80/person), hotel ($400/ person).
Equipment			
Computers		$1000.00	To purchase one computer (if eligible)
Knowledge Dissemination/Mobilization			
Knowledge Dissemination/ Mobilization		$20,053	1. Abstract submission for three posters or presentations ($105) 2. Poster printing costs for three posters ($300) 3. Conference registration for three team members ($3000) 4. Contribution toward travel, accommodation and food allowance for three team members to attend a conference ($4500) 5. Open Access journal fees for two publications ($12,148); other papers can be published in journals without fees.
Total			**$130,090.00**

TIP

The sample budget above was developed anticipating eight months of guideline development work. We found a coordinator was needed for closer to a year in order to coordinate the review and guideline publication process.

Section 2: Establishing a guideline development team (GDT) and preparing for its tasks

In this section of the manual, the first stage of guideline development is described. The first step involves establishing a timeline with deadlines that are both realistic and match funding requirements. Next you should establish the GDT and complete preparation that will lay the ground work for all future tasks.

Main Steps:

2.1 Establish a guideline development timeline
2.2 Review the budget
2.3 Determine GDT composition
2.4 Target and recruit GDT members, collaborators and support staff
2.5 Perform a scoping review of the literature
2.6 Hold a face-to-face team meeting

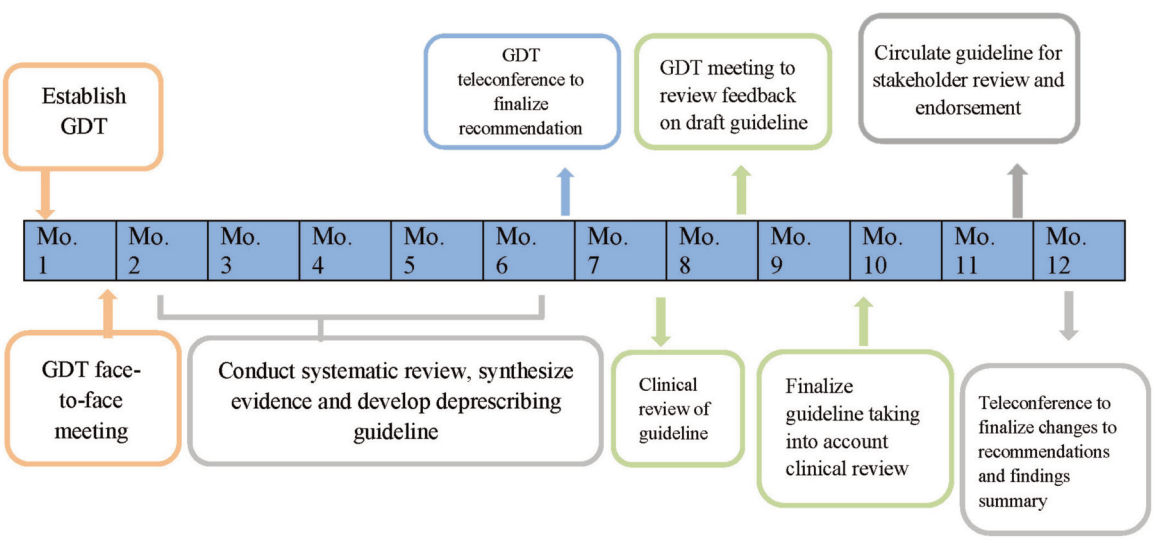
2.1 Establish a guideline development timeline

Along with the guideline lead, estimate how long it will take to:

1. Form a GDT
2. Decide on an explicit scope for the guideline
3. Collect the evidence in the literature to inform a decision
4. Analyze the literature to determine a recommendation
5. Finalize the recommendation within the team
6. Conduct clinical and stakeholder reviews

In our experience, development of a deprescribing guideline requires approximately one year from start to finish with a dedicated team. Timelines will vary by project. It is important to provide them to team members during the recruitment process and to establish realistic deadlines from the outset that match funding amounts and end dates.

Sample timeline:



2.2 Review the budget

Once your timeline has been drafted, you may wish to review and modify the budget, perhaps in conjunction with the next step.

2.3 Determine GDT composition

The composition of the GDT should be established based on the medication class and intended audience of the guideline. The team should have a member from each professional group that will use the guideline, most likely:

- Family physicians
- Pharmacists
- Nurse practitioners
- Long-term care physician, internist or a geriatrician (depending on the target population)
- Methodologist
- Patient (may not be necessary for all medication classes, although patient engagement in research processes becoming increasingly recognized)

Additionally, specialists whose advice would be sought for clinical decision-making relating to the topic of interest should be included as well. For example, a geriatric psychiatrist was included in the antipsychotics deprescribing guideline and a gastroenterologist on the proton pump inhibitor team. It is strongly recommended to have a member with systematic review methodology expertise and preferably also GRADE expertise on the team, to help the group with translating evidence into recommendations.

It is possible that the project lead will act as the GDT lead, or the GDT will identify the lead during its first meeting. Typically, the GDT lead will have clinical expertise in the selected area and be willing to take responsibility for ensuring all guideline development and review steps are completed in a timely fashion, with the guideline coordinator's support. We highly recommend that the GDT lead and the guideline coordinator be co-located to facilitate timely discussion and decision-making.

TIP

Volunteers for the guideline lead position need to understand their role and responsibility in driving deliverables and meeting timelines. Strong leadership is essential.

Additionally, collaborators (such as a statistician for data analysis of systematic review) can be very valuable members of a GDT and should be considered as needed.

2.4 Target and recruit GDT members, collaborators and support staff

2.4.1 Target and recruit GDT members

Recruit members from existing networks (e.g., Cochrane collaboration), known experts in the clinical field (e.g., those involved in prescribing guidelines for the clinical topic), enquiring through professional organizations, or via other means. The main provision for membership should be that the individual bring a justifiable content and/or methodological expertise to the group. It is helpful to avoid people with significant conflicts of interest from the beginning.

TIP

There has been a lot of interest from primary care because of our inclusion of family physicians on the guideline development teams.

Because most of these guidelines will be used by primary care practitioners, it is helpful to have more than one on the team, but to still include at least one specialist in the clinical area.

As far as budget will allow, attempt to engage members from across the country. Keep in mind that a diverse field of team members with varying opinions will ensure all viewpoints are considered.

Sample GDT member recruitment email (used to invite potential members to be part of the antihyperglycemics deprescribing guideline development team):

Dear

We are creating a Guideline Development Team (GDT), whose goal will be to develop an evidence-based deprescribing guideline for antihyperglycemic medications.

I would like to formally invite you to join this team. The team will include pharmacists, geriatricians, nurse practitioners, epidemiologists, family physicians and long-term care physicians, as well as guideline development (GRADE methods) experts. We anticipate that the guideline development process will begin in June 2015 and be completed by December 2015.* Your role would be to share your expertise and to support the development of the research questions and other research parameters, and also to help us analyze the literature on various deprescribing strategies for antihyperglycemic medications. We are planning a face-to-face meeting of the team in Ottawa on June 15, 2015, from 11 am to 4 pm. Thereafter, the team will likely meet by teleconference two or three additional times (shorter meetings than the first) to review progress and vote on final recommendations.

We believe you could make valuable contributions to the team, and hope that you will consider accepting our invitation.

Please let us know if you are interested in this opportunity and we will be in touch with further details.

TIP

*Originally it was anticipated a guideline could be developed in six months; we discovered it takes much longer, closer to a year.

2.4.2 Recruit support staff and collaborators

Collaborators other than GDT members and additional support staff can be very valuable members of a GDT and should be considered as needed. You may consider recruiting a librarian, statistician, pharmacy resident and medical student to help with the tasks related to knowledge gathering and synthesis, such as the systematic review or various scoping reviews.

2.4.3 Document conflicts of interest

It is useful to enquire regarding potential pharmaceutical manufacturer conflicts of interest when screening potential GDT members. Inform potential members that there is a requirement to disclose all potential conflicts, and ensure they are comfortable with focusing the guideline on weighing benefit/harm of continuing a medication versus deprescribing it.

Each GDT member must complete and submit a conflict of interest form at the beginning (either prior to or at the first GDT meeting) and again pre-publication.

Sample disclosure form:

Deprescribing Guideline Development Team and Collaborators
Disclosure Form

Preamble:

This disclosure form will be completed by members prior to each in-person meeting to provide information on financial, business/professional and intellectual potential competing interests related to the topics addressed. GDT members, as well as collaborators and support persons, are expected to provide full disclosure for new topics, and an updated disclosure reflecting changes in their situation since the form was last completed, for continuing topics. The disclosure form will also be completed by new members prior to their participation. Completed disclosure forms will be kept on file in the Deprescribing Research Team office.

Name: _____

I have reviewed my current activities and those of recent years for potential conflict of interest that would impair the scientific integrity of the work of the Deprescribing Guideline Development Team, including financial (to include clinical practice that would benefit from a specific guideline topic under development), intellectual, affiliations or memberships in Associations, research funding, payments, gifts, gratuities, honoraria, advocacy, consulting or other conflicts.

I would like to bring the following to the attention of other members of the Deprescribing Guideline Development Team (check appropriate box and provide details below):

Guideline Name	Financial	Intellectual	Affiliations/ Memberships	Research Funding	Payments/Gifts	Advocacy	Consulting	Others

Details:

I hereby certify that I am not in a position of real, potential or apparent conflict of interest except as disclosed above. I undertake to inform the Deprescribing Guideline Development Team lead of any changes in circumstances that may place me in a position of real, potential or apparent conflict of interest.

Signature_____ Date_____

2.5 Perform a scoping review of the literature

A scoping review will help estimate the feasibility of developing the guideline and the workload involved. It may be completed by the guideline coordinator while GDT members are being recruited, or may have been done prior to proposal submission. If the latter, it should be updated prior to the first GDT meeting. The scoping review is intended to answer the following questions:

1. What literature has been published on the deprescribing of the drug class of interest?
2. What reviews, systematic reviews and meta-analyses have been published examining the benefits and/or harms of the drug class of interest?

A good understanding of the breadth and focus of the literature surrounding those two questions will provide a solid starting point for the GDT to determine whether sufficient evidence exists to guide a recommendation, how they should structure their research question(s) (e.g., the most relevant indications and patient-important outcomes) and direct their work (e.g., will the group need to perform a de novo systematic review or is there existing work that can be used?). The results of the scoping review will be presented at the first GDT face-to-face meeting.

Examples of a scoping review methodology and search strategy follow.

Sample of scoping review methodology:

The methodology for this scoping review was based on Arksey & O'Malley and Armstrong et al, and employed the following steps: identify the research question, identify relevant studies, study selection, charting the data, collating and summarizing and reporting the results.[i-iii]

Research question

The research questions were based on previous deprescribing guideline scoping review questions for PPIs and with the goal of identifying studies and/or existing systematic reviews that investigate deprescribing of BZRAs as well as harms/benefits of continued BZRA use. The questions were reviewed by the deprescribing guideline team and reviewed by the BZRA deprescribing team lead before a search strategy was refined and search conducted.

Identifying relevant studies

Search strategies were based on those of the previously conducted PPI deprescribing scoping review. For the BZRA deprescribing scoping review, the search strategies were further reviewed and modified in conjunction with a librarian from the Canadian Library of Family Medicine (CLFM). The search strategy for both questions follows this methodology discussion. The search strategy for question 1 has been modified and reviewed by the CLFM librarian, while the search strategy for question 2 is preliminary and awaits final review by the CLFM librarian. As per the sample search strategy, the following databases were searched: PubMed, Cochrane Library, PsychINFO and EMBASE. A bibliographic search of select systematic reviews was also conducted to identify further studies.

Study selection

Abstracts and titles were screened by 1 reviewer. Inclusion criteria include: 1) study type: guideline, systematic review/meta-analysis, randomized controlled trial or large observational study; 2) indication for BZRA: insomnia; 3) involves any deprescribing intervention (e.g., substitutive medication, patient education, cognitive-behavioural therapy [CBT], etc.); 4) age: adults > 18 years of age (though search strategy specified older persons, we selected studies with adult patients of any age)

References

i) Arksey H, O'Malley L. Scoping studies: Towards a Methodological Framework. *Int J Soc Res Methodol.* 2005;8:19-32.

ii) Armstrong R, Hall BJ, Doyle J, Waters E. 'Scoping the scope' of a Cochrane review. *J Public Health* (2011) 33 (1):147-50.

iii) Joanna Briggs Institute. The Joanna Briggs Institute Reviewers' Manual 2015: Methodology for JBI Scoping Reviews. Australia: Joanna Briggs Institute, 2015. Available: https://joannabriggs.org/assets/docs/sumari/Reviewers-Manual_Methodology-for-JBI-Scoping-Reviews_2015_v2.pdf (accessed Feb. 19,2018).

Sample scoping review search strategy:

QUESTION 1: What literature exists on deprescribing of benzodiazepine receptor agonists (BZRAs)?
KEYWORDS FOR 1st CONCEPT: deprescribing deprescrib* OR de-prescrib* OR ceas* OR withdraw* OR stop* OR cessation OR discontinu* OR reduc* OR taper* OR eliminat* OR decreas*
KEYWORDS FOR 2nd CONCEPT: benzodiazepines + z drugs benzodiazepine* OR alprazolam OR bromazepam OR clonazepam OR diazepam OR flumazenil OR flunitrazepam OR flurazepam OR lorazepam OR nitrazepam OR oxazepam OR temazepam OR chlordiazepoxide OR midazolam OR triazolam OR clorazepate OR nordazepam OR prazepam OR zopiclone OR eszopiclone OR zaleplon OR zolpidem OR benzodiazepine [MeSH terms]
KEYWORDS FOR 3rd CONCEPT: over 65 benzodiazepine* OR alprazolam OR bromazepam OR clonazepam OR diazepam OR flumazenil OR flunitrazepam OR flurazepam OR lorazepam OR nitrazepam OR oxazepam OR temazepam OR chlordiazepoxide OR midazolam OR triazolam OR clorazepate OR nordazepam OR prazepam OR zopiclone OR eszopiclone OR zaleplon OR zolpidem OR benzodiazepine [MeSH terms]
QUESTION 2: What are the benefits and harms of BZRAs?
KEYWORDS FOR 1st CONCEPT: benzodiazepines + z drugs benzodiazepine* OR alprazolam OR bromazepam OR clonazepam OR diazepam OR flumazenil OR flunitrazepam OR flurazepam OR lorazepam OR nitrazepam OR oxazepam OR temazepam OR chlordiazepoxide OR midazolam OR triazolam OR clorazepate OR nordazepam OR prazepam OR zopiclone OR eszopiclone OR zaleplon OR zolpidem OR benzodiazepine [MeSH terms] OR hypnotics and sedatives [MeSH terms]
KEYWORDS FOR 2nd CONCEPT: harms/benefits benefit* OR effective* OR efficacy OR risk OR risks OR risky OR harm* OR effects OR safety
KEYWORDS FOR 2nd CONCEPT: harms/benefits Limit study type to systematic review: systematic [sb]

2.6 Hold a face-to-face team meeting

Ideally, a face-to-face team meeting should be scheduled, in which the GDT is introduced to each other and steps 2.6.1 and 2.6.2 are accomplished. Though a teleconference can be substituted here, experience has shown that an in-person meeting is an ideal way for members to meet each other, establish an agreed-upon guideline scope and encourage collaboration and productivity. A sample agenda for the first face-to-face meeting is outlined below. Specific actions and attachments will be described in more detail following.

Sample agenda for initial meeting:

Time	Item	Leader	Action/Decision Required	Attachments
11:00	Approve agenda		Add items if needed	
11:00 11:30	Welcome and overview		- Deprescribing project overview - Introductions - Introduce roles for members	Roles and responsibilities document
11:30 11:45	Lessons learned		Review lessons learned from previous guideline development processes, including algorithms used to summarize guidelines*	- PowerPoint - Algorithms
11:45 12:30	Scoping exercise		Present results of the scoping exercises	Scoping exercise results chart
12:30 1:15			**Lunch Break**	
1:15 2:40	Refine population, intervention, comparator, outcomes (PICO) and clinical context questions for guideline development		Discuss evidence from scoping review; refine and agree on scope of guideline including: 1. Research questions (PICO and clinical context)** 2. Relevant outcomes 3. Approach for literature searches and synthesis of evidence for guideline Determine clinical consideration components***	PowerPoint
12:30 1:15			Lunch Break	
2:50 3:35	Guideline management, tasks and timeline		Approve guideline template Assign GDT members, contributors and staff to specific tasks	- Draft guideline template - Roles and responsibilities document
3:35 3:50	Dissemination plan		Discuss dissemination options (target conferences and journals)	
3:50	Meeting dates/-times		Determine dates/times for team meetings	Draft timeline chart
4:00			**Meeting Adjourned**	

TIP

*For our first guideline, we produced a decision-making algorithm based on the guideline as a knowledge translation tool after the guideline was complete. But, the algorithm turned out to be the most effective tool. So, for subsequent guidelines, we drafted the algorithm as we went along. This helped us to identify important exclusion criteria, as well as tapering and monitoring parameters and what alternatives to recommend.

Read Section 5.1 before going any further.

TIP

**Clinical context questions are those that inform the GRADE rating of the guideline recommendation – including patient values and preferences, review of benefits and harms of continuing the drug, and resource implications.

TIP

**Clinical consideration questions are those that address clinicians' questions about how to taper medication doses, and what to expect in terms of adverse drug vwithdrawal events.

2.6.1 Determine the scope of the guideline and particular PICO questions for systematic review

After presenting the team with the results from the initial scoping review, the group should collectively decide on the scope of the guideline. This should include formulating research questions with Population, Intervention, Comparator and Outcomes (PICO) details.

TIP

This step is very important in order to keep the systematic review focused.

At this stage, the team will also need to decide whether a systematic review will need to be performed to answer the research questions or whether sufficient synthesis of the evidence has already been performed for the purposes required. Should an outdated systematic review exist, an update is necessary.

Sample of PICO questions from previous deprescribing guidelines:

Topic	Main PICO Question
Proton pump inhibitors (PPIs)	In adults, what are the effects (harms and benefits) associated with deprescribing long-term daily PPI therapy compared to continuous and chronic use?
Benzodiazepines (BZRAs)	What are the effects (benefits and harms) of deprescribing BZRAs compared to continued use in adults with insomnia?
Antipsychotics	What are the effects (harms and benefits) associated with deprescribing compared to continuation of antipsychotic medication for the treatment of BPSD in adults?
Antihyperglycemics	In adults with type 2 diabetes, what are the effects (benefits and harms) of deprescribing antihyperglycemics compared to continuous use of antihyperglycemics?

Sample of clinical consideration questions from previous deprescribing guidelines:

1. How can patients be engaged in the deprescribing process?
2. How should tapering be approached?
3. What should be monitored and how often?
4. How to manage recurring symptoms?
5. What factors warrant continued use?

2.6.2 Assign roles and responsibilities

Guideline development tasks should be well described during the first GDT meeting, listing all duties required for completion of the guideline manuscript. Sample manuscripts of other deprescribing guidelines can be shared to help GDT members understand the workload involved. The team members are asked to commit to those tasks in which they are interested until all are assigned. Typically, the systematic review is completed by the guideline coordinator with one or two other collaborators (e.g., a pharmacy resident, trainee or committed GDT member). The review of review of harms is typically completed by a GDT member with the assistance of a trainee, and/or the guideline coordinator. Other literature searches for remaining contextual questions and clinical considerations are completed by a librarian and screened by the guideline coordinator. The guideline coordinator will work with the librarian to provide team members with the most relevant literature to summarize for narrative components of the guideline. It is helpful to explain to members that their workload is primarily in summarizing key literature to contribute to recommendations for the guideline, and that the guideline coordinator is there to make this work efficient and feasible. For example, the guideline coordinator can place relevant literature in a Dropbox for GDT members, facilitate group discussions when several people are working on one section and help by providing timelines.

TIP

When two or three people agree to write a section together, it is helpful to have one person act as the lead to work with the coordinator in setting timelines and determining meeting dates.

Sample of roles and responsibilities task list:

Activity	Details	Most Responsible Person(s)	Support Staff	Expect Date of Completion	Status
Scoping review					
PICO summary and approval					
Consult with librarian re: search strategies					
Systematic review protocol and review					
Guideline Components					
Introduction					
Key points					
Scope					
Methods					
Summary of findings and quality of evidence					
GRADE review					
Values and preferences (patient, family, staff and care-givers)					
Review of review of harms					
Resource implications and cost-effectiveness					
Recommendations					
Clinical considerations					
Comparison to other guidelines					
Conclusion					
References					
Guideline Revisions					
Clinical review and revisions as needed					
Stakeholder review and revisions as needed for endorsement					
Implementation					
Publication					
Algorithm					
Identify other tools useful for practitioners					

Section 3: Drafting the guideline

Following the face-to-face meeting, the main PICO question for systematic review and the clinical context question will have been set. The next step in the guideline development process is to begin synthesizing all of the evidence that will form the guideline evidence base, and serve to formulate a final recommendation to be voted on by the GDT. The systematic review can be conducted by staff and/or students, in consultation with methods and GRADE experts. The librarian will help develop and execute search strategies, then staff will provide GDT members with literature relevant to their assigned topic for reading as described above. Each GDT member or group will write their section of the guideline based on this literature review. Each section will be summarized in an evidence-to-recommendations table, which will guide the creation of the final recommendation to be voted on.

Main Steps:

3.1 Devise search strategies
3.2 Conduct the systematic review for the PICO question
3.3 Conduct a review of benefits of continuing the drug class and a review of review of harms of continuing the drug class
3.4 Conduct literature review of contextual questions
3.5 Assess certainty/quality of evidence using GRADE
3.6 Develop an evidence-to-recommendations table
3.7 Draft recommendations and conduct GDT voting
3.8 Compile evidence, additional information and recommendations into guideline draft

3.1 Devise search strategies

Clinical recommendations require identifying, analyzing and weighing the evidence in several areas: the direct research questions pertaining to the scope of the guideline (i.e., clinical evidence of benefits/harms of deprescribing and of continued use of the drug/drug class); the values and preferences of health care providers, patients, family members and caregivers pertaining to the drug(s)/condition(s) of interest, and the resources and costs relating to the treatment. Additionally, the guideline will have to be compared with other guidelines recommending treatment strategies in the area of interest. Each of these topic areas requires its own literature search.

Devise a search strategy, in consultation with a librarian if possible, for:

- The systematic review of deprescribing studies of the drug class if one does not already exist
- The review of reviews of harms
- Each contextual question (e.g., resource implications, patient values and preferences)

Librarians can help structure and perform these searches if they're involved with the project. Consider having the search strategies peer-reviewed by a second librarian using the PRESS Checklist if the intention is to publish the systematic review as a separate paper.[6] Alternatively, a central project staffer can perform the work. Lastly, and perhaps least efficiently, the members of the GDT tasked with each of the topics can perform the search related to their specific topic(s).

3.2 Conduct the systematic review for the PICO question

The systematic review is necessary to identify research that has been completed regarding the outcomes (both benefits and/or harms) of deprescribing a drug or drug class. The systematic review question will have been determined previously, at the first GDT meeting.

If the scoping review of the literature revealed previously conducted, high quality[7] and up-to-date published systematic reviews, and/or meta-analyses consistent with the PICO question(s), they can be used for the guideline. However, if no such review exists for any PICO question, or if a review exists that only includes part of the defined inclusion and/or exclusion criteria for a PICO question, a systematic review of the literature will be needed.

When developing the systematic reviews for the deprescribing project, follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[4]. The Cochrane Handbook is also useful as a guide.

The first step is to develop and register a protocol. The PRISMA-P statement outlines the process for developing a systematic review protocol.[8] Protocols can be registered at PROSPERO (www.crd.york.ac.uk/PROSPERO/). As one example, the protocol for the antihyperglycemic deprescribing systematic review can be found in the references.[9]

For a detailed method on writing a systematic review please see the Cochrane Handbook[3] and PRISMA statement.[4] For a detailed checklist on how to report and conduct your systematic review please see the PRISMA statement (www.prisma-statement.org/).

Keep a running authorship table to document who has contributed and in what capacity for systematic review publication (see the following example).

TIP

Depending on how long the guideline process takes, it may be necessary to update the literature search for the systematic review to ensure any recent trials are captured.

	CONDITION FOR AUTHORSHIP							OTHER CONTRIBUTIONS WORTHY OF ACKNOWLEDGEMENT	FOR OFFICE USE ONLY	
Team Members (Past and Current)	Condition 1 (only 1 of 3 necessary to meet condition)					Condition 2	Condition 3	Please Elaborate (e.g., collected data, scientific advisor, site recruitment)	Offer of authorship/ acknowledgement made to team members Sign-off (authorship/ acknowledgement accepted)	
	Conception and Design		Acquisition of Data (Instrument design/data collection)		Analysis and Interpretation of Data	Drafting the Article/ Critical Revision for Important Intellectual Content	Final Approval of the Version to be Published			
	Initial	On-going	Initial	Final						
Current Members										
Past Members										

TIP

In some cases, we submitted our systematic review protocols and results to Cochrane. Their review times can be lengthy and we needed to move ahead with recommendations and guideline writing before Cochrane feedback was received. Consider alternate methods for systematic review protocol and publication that may be more efficient.

3.3 Conduct a review of benefits of continuing the drug class and a review of review of harms of continuing the drug class

In making recommendations for deprescribing, GDT members also need to consider the potential benefit of continuing a medication. This may have been considered early on in the selection of the population to whom the guideline applies (e.g., by excluding patients for whom benefit of continuing is very clear) or by including a section within the guideline manuscript that succinctly outlines the benefits as taken from national guidelines.

The harms of taking the target class of medication are ideally summarized as review of reviews of harms.[10,11] The search strategy will be executed by the guideline coordinator who will then review the relevant literature, ideally with the help of available support staff, and provide the lead authors of this section with the relevant literature.

Sample of review of harms search for the antihyperglycemic deprescribing guideline (completed August 7, 2017):

Search Methods: Harms

A sensitive search was conducted to retrieve papers on the harms, side effects and adverse effects of antihyperglycemic agents. Medline via OVID, and Cochrane Library via Wiley August 7, 2015. Study design filters for harms were applied [Golder S, McIntosh HM, Loke Y. Identifying systematic reviews of the adverse effects of health care interventions. BMC Medical Research Methodology 2006;6:22.][BMJ Clinical Evidence. Search filters. BMJ. 2006. Available at: www.clinicalevidence.com/x/set/static/ebm/learn/665076.html (accessed 7 August 2015).]

A validated systematic review filter was also applied.[Montori VM, Wilczynski NL, Morgan D, Haynes RB. Optimal search strategies for retrieving systematic reviews from MEDLINE: analytical survey. BMJ 2005;330(7482):68. [Ovid/PubMed] Also athttp://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx]

No date limits were applied. 965 abstracts were retrieved and 772 were retained after a manual de-duplication of the records in Reference Manager.

Database, Platform and Timespan	Search Date	Results
Cochrane Library 2015 Issue 6 CDRS DARE	August 7, 2017	34
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>	September 3, 2017	808
	Total Results	**965**
	Total After Duplicates Removed	**772**

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

---

1 Hypoglycemic Agents/ad, ae, tu, th, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Therapy, Toxicity] (34130)
2 (antihyperglycemic or anti-hyperglycemic).ti,ab. (1764)
3 Metformin/ad, tu [Administration & Dosage, Therapeutic Use] (5916)
4 Sulfonylurea Compounds/ad, tu [Administration & Dosage, Therapeutic Use] (2952)
5 (Meglitinides or Sulfonylurea).ti,ab. (4626)
6 Glyburide/ (5747)
7 glyburide$.ti,ab. (1369)
8 Thiazolidinediones/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (4518)
9 (Glitazones or TZD*).ti,ab. (1924)
10 Dipeptidyl-Peptidase IV Inhibitors/ (2025)
11 Glucagon-Like Peptide 1/ (5458)
12 Insulin/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy] (32891)
13 Insulin, Long-Acting/ or Insulin, Short-Acting/ (2524)
14 or/1-13 (73053)
15 (ae or to or po or co).fs. (3313524)
16 (safe$ or risk$).ti. (436833)
17 side effect$.ti,ab. (189308)
18 ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab. (351899)
19 exp product surveillance, postmarketing/ (12120)
20 exp adverse drug reaction reporting systems/ (6052)
21 exp clinical trials, phase iv/ (233)
22 exp poisoning/ (136720)
23 exp drug toxicity/ (93276)
24 exp abnormalities, drug induced/ (14266)
25 exp drug monitoring/ (15457)
26 exp drug hypersensitivity/ (39752)
27 (toxicity or complication$ or noxious or tolerability).ti,ab. (966305)
28 or/15-27 (4409578)
29 14 and 28 (26763)
30 (MEDLINE or systematic review).tw. or meta analysis.pt. (140768)
31 29 and 30 (808)

Cochrane Library

Cochrane Database of Systematic Reviews, Database of Reviews of Effectiveness
Search Name:Antihyperglycemics review - harms
Last Saved:07/08/2015 17:02:14.194
Description:

IDSearch

#1[mh "Hypoglycemic Agents"]
#2(antihyperglycemic or anti-hyperglycemic):ti,ab

#3[mh Metformin]
#4[mh "Sulfonylurea Compounds"]
#5(Meglitinides or Sulfonylurea):ti,ab
#6[mh Glyburide]
#7(glyburide*):ti,ab
#8[mh Thiazolidinediones]
#9(Glitazones or TZD*):ti,ab
#10[mh "Dipeptidyl-Peptidase IV Inhibitors"]
#11[mh "Glucagon-Like Peptide 1"]
#12[mh Insulin]
#13[mh "Insulin, Long-Acting"]
#14[mh "Insulin, Short-Acting"]
#15{or #1-#14}
#16(safe* or risk*):ti
#17(side next effect*):ti,ab
#18((adverse or undesirable or harm* or serious or toxic) near/3 (effect* or reaction* or event* or outcome*)) .ti,ab.
#19[mh "product surveillance, postmarketing"]
#20[mh "adverse drug reaction reporting systems"]
#21[mh poisoning]
#22[mh "drug toxicity"]
#23[mh "abnormalities, drug induced"]
#24[mh "drug monitoring"]
#25[mh "drug hypersensitivity"]
#26(toxicity or complication* or noxious or tolerability):ti,ab
#27{or #16-#26}
#28#15 and #27

TIP

Results of the review of review of harms should be summarized in a table including ranges of frequency ratios for harms.

3.4 Conduct literature review of additional contextual questions

TIP

Clinical context questions are those that inform the GRADE rating of the guideline recommendation — including review of benefits and harms, patient values and preferences, and resource implications.

Patient values and preferences, and resource implications, are examples of additional contextual questions. Relevant literature should be supplied to team members responsible for their respective guideline sections requiring a literature review. The search strategy for each contextual question will be executed by the librarian or guideline coordinator, who will then review the results, ideally with the help of available support staff, and provide the

lead authors of the section with the relevant literature. The authors of these sections should be directed to analyze the literature and produce a narrative synthesis that can be included in the guideline. This process can happen concurrently with the systematic review and GRADE process.

Sample search methods: Patient perspectives (completed August 24, 2017)

A sensitive search was conducted to retrieve papers on patient issues and perspectives of treatment with antihyperglycemic agents. Medline via OVID was searched from 1946 to present. An adapted study filter for patient perspective issues was applied [SIGN - patient issues [undated] [Ovid] ISSG search filter appraisal Available at: http://www.sign.ac.uk/methodology/filters.html#patient (accessed 20 August 2015).] [Wessels, M, Hielkema, L. How are we feeling today? The sensitivity of a literature search filter for patients' values and preferences. BMJ Quality and Safety, 2013. 22; Suppl 1:A33.2.]

No date limits were applied; 1186 abstracts were retrieved.

Database, Platform and Timespan	Search Date	Results
Database, Platform and Timespan	August 24, 2017	1186
	Total Results	**1186**

Page Break Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

---

1 *patient acceptance of health care/ (18723)
2 *Patients/ed, px (4621)
3 *persons/ed, px (0)
4 *family/ed, px (10201)
5 *Consumer Participation/ (8067)
6 *Patient Satisfaction/ (22087)
7 (choice$ or empower$).ti. (32659)
8 (qualitative or ethnon* or ethnograph* or participant observ* or focus group* or grounded theory or narrative analysis or lived experience* or life experience* or theoretical samp* or action research).ti. (30112)
9 ((patient or patients or amputee* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj3 (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or symptom or symptoms or limitations or survey* or lives or burden or attitude* or belief* or knowledge or lessons or reaction* or motivation* or intention* or involv* or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding)).ti. (47808)

10 (acceptance or acceptability or quality of life or satisfaction or compliance or adherence or cooperation or co-operation or nonadherence or noncompliance or interview*).ti. (148971)

11 ((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj3 (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or acceptance or acceptability or limitations or survey* or lives or interview* or quality of life or satisfaction or burden or attitude* or belief or knowledge or lessons or reaction* or motivation* or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or compliance or adherence or cooperation or co-operation or nonadherence or noncompliance)).ab. /freq=2 (69748)

12 patient*.jw. (11634)

13 or/1-12 (350037)

14 Diabetes Mellitus/dt (13647)

15 Diabetes Mellitus, Type 2/dt (23095)

16 Diabetes Mellitus, Type 1/dt (11675)

17 Hypoglycemic Agents/ad, ae, tu, th, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Therapy, Toxicity] (34278)

18 (antihyperglycemic or anti-hyperglycemic).ti,ab. (1772)

19 Metformin/ad, tu [Administration & Dosage, Therapeutic Use] (5955)

20 Sulfonylurea Compounds/ad, tu [Administration & Dosage, Therapeutic Use] (2957)

21 (Meglitinides or Sulfonylurea).ti,ab. (4636)

22 Glyburide/ (5750)

23 glyburide$.ti,ab. (1368)

24 Thiazolidinediones/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (4526)

25 (Glitazones or TZD*).ti,ab. (1934)

26 Dipeptidyl-Peptidase IV Inhibitors/ (2043)

27 Glucagon-Like Peptide 1/ (5495)

28 Insulin/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy] (32950)

29 Insulin, Long-Acting/ or Insulin, Short-Acting/ (2539)

30 or/17-29 (73281)

31 or/14-16 (45689)

32 13 and 30 and 31 (1186)

33 from 32 keep 1-1186 (1186)

Sample search methods: Resource implications and cost effectiveness (completed September 3, 2017)

A sensitive search was conducted to retrieve papers on resource implications and cost-effectiveness of treating diabetes in the elderly and the resource implications of hypoglycemia in the elderly. Economic Evaluation Database via Cochrane Library and Medline via OVID was searched from 1946 to present. A validated study filter for health economics was applied in Medline. [Wilczynski NL, Haynes RB, Lavis JN, Ramkissoonsingh R, Arnold-Oatley AE, HSR Hedges team. Optimal search strategies for detecting health services research studies in MEDLINE. Canadian Medical Association Journal 2004;171(10):1179-85. [Ovid]. Available at: http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx]

No date limits were applied. 1582 titles and abstracts were retrieved. 1313 were retained after duplicates were removed.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Database, Platform and Timespan	Search Date	Results
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>	September 3, 2017	1332
Economic Evaluation Database EED via Cochrane Library Issue 8 2015	September 3, 2017	250
	Total Results	**1582**
	Total After Duplicates Removed	**1313**

Search Strategy:

---

1 *Diabetes Mellitus/dt (6782)
2 *Diabetes Mellitus, Type 2/dt (16038)
3 *Diabetes Mellitus, Type 1/dt (6725)
4 or/1-3 (28365)
5 *Hypoglycemic Agents/ec (266)
6 (antihyperglycemic or anti-hyperglycemic).ti,ab. (1783)
7 Metformin/ad, tu [Administration & Dosage, Therapeutic Use] (6037)
8 Sulfonylurea Compounds/ad, tu [Administration & Dosage, Therapeutic Use] (2979)
9 (Meglitinides or Sulfonylurea).ti,ab. (4659)
10 Glyburide/ (5763)
11 glyburide$.ti,ab. (1372)
12 Thiazolidinediones/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (4566)
13 (Glitazones or TZD*).ti,ab. (1950)
14 Dipeptidyl-Peptidase IV Inhibitors/ (2073)
15 Glucagon-Like Peptide 1/ (5551)
16 Insulin/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy] (33079)
17 Insulin, Long-Acting/ or Insulin, Short-Acting/ (2554)
18 or/5-17 (61145)
19 exp "costs and cost analysis"/ (193294)
20 (costs or cost effective:).tw. (211079)
21 (cost: or cost benefit analys: or health care costs).mp. (492267)
22 Drug Prescriptions/ec, st, td, ut [Economics, Standards, Trends, Utilization] (5221)

23 ((inappropriate or appropriate) adj3 prescri*).ti,ab. (2798)
24 Health Services/ec, es, ma, st, td, ut [Economics, Ethics, Manpower, Standards, Trends, Utilization] (11718)
25 or/19-24 (514835)
26 Hypoglycemic Agents/ec [Economics] (715)
27 Metformin/ec (73)
28 Sulfonylurea Compounds/ec (36)
29 Glyburide/ec (14)
30 Thiazolidinediones/ec (59)
31 Dipeptidyl-Peptidase IV Inhibitors/ec (21)
32 Glucagon-Like Peptide 1/ec (17)
33 Insulin/ec (387)
34 Insulin, Long-Acting/ec or Insulin, Short-Acting/ec (45)
35 or/26-34 (877)
36 4 and 18 and 25 (777)
37 35 or 36 (1332)

Search Name: Antihyperglycemics review – EED results exported
Last Saved:07/08/2015 17:02:14.194

Description:
IDSearch
#1[mh "Hypoglycemic Agents"]
#2(antihyperglycemic or anti-hyperglycemic):ti,ab
#3[mh Metformin]
#4[mh "Sulfonylurea Compounds"]
#5(Meglitinides or Sulfonylurea):ti,ab
#6[mh Glyburide]
#7(glyburide*):ti,ab
#8[mh Thiazolidinediones]
#9(Glitazones or TZD*):ti,ab
#10[mh "Dipeptidyl-Peptidase IV Inhibitors"]
#11[mh "Glucagon-Like Peptide 1"]
#12[mh Insulin]
#13[mh "Insulin, Long-Acting"]
#14[mh "Insulin, Short-Acting"]
#15{or #1-#14}

3.5 Assess certainty/quality of evidence using GRADE

TIP

Refer to most recent GRADE approach regarding whether to use “quality” or “certainty” of evidence. The deprescribing guidelines used ‘quality’ but GRADE has been working on changing to an assessment of “certainty.”

Grading of recommendations assessment, development, and evaluation (GRADE) is a structured and rigorous process for rating the quality or certainty of evidence in a systematic review and to formulate recommendations from this evidence (including the strength of the recommendation.[5] The process is summarized in more detail by Guyatt et al.[5] GRADE resources are available free from the GRADE website, including GRADE pro software download (www.gradeworkinggroup.org/index.htm).

The systematic review used to answer the primary research (PICO) question of the guideline is used to complete the GRADE assessment. This systematic review could be completed *de novo* for the purpose of the guideline, or an existing systematic review answering the guideline's primary question can be used. The GRADE assessment is conducted after the systematic review is complete and is based on the outcomes decided a *priori* by the GDT.

3.5.1 Form the GRADE team

Determine who will be responsible for conducting the GRADE assessment. The GDT should include a methodologist or guideline expert familiar with using GRADE methodology. This GDT member will complete a GRADE assessment with the support and assistance of the guideline coordinator.

Alternatively, the guideline coordinator can do the GRADE assessment under the supervision of, and in consultation with, this GDT member. This may depend on the comfort/proficiency of the coordinator in using GRADE methodology and the availability of the GDT member to complete this task in a timely manner. The decision regarding who will complete the GRADE assessment should be made early on in the guideline development process, ideally at the initial meeting.

In the case where the coordinator is merely supporting the GDT member in doing the GRADE assessment, the coordinator should still have a general understanding of the methodology behind the GRADE approach to be able to support the GDT member. In this case, the coordinator may be responsible for providing systematic review data to the GDT member and generating summary-of-findings tables.

3.5.2 Read background documents on GRADE process and become familiar with GRADEpro software

The coordinator should become familiar with GRADE methodology using the GRADE website resources listed above, as well as chapter 12.2 of the Cochrane Handbook for Systematic Reviews of Evidence, which includes details on assessing quality of evidence.[3] These are excellent resources that outline the entire GRADE process, and provide practical advice and guidance. The coordinator may also learn how to use the GRADEpro software available from the GRADE website listed above.

3.5.3 Compile electronic files with necessary articles and systematic review/meta-analysis file

The coordinator should compile the PDFs of all of the articles that will be assessed. The systematic review file (created via Revman: http://tech.cochrane.org/revman) will also be required to conduct GRADE. These files can then be sent to the GDT member completing the GRADE assessment.

3.5.4 Conduct GRADE assessment and generate summary-of-findings table

The GDT member and/or coordinator will complete the GRADE assessment using GRADEpro software and the Revman file provided. The primary output of the GRADE assessment is the quality of evidence rating, as well as the summary-of-findings table and quality-of-evidence table[12] that support and provide rationale for the evidence rating. The GDT member and/or coordinator will provide the GDT with a summary-of-findings table and a quality-of-evidence table that can be used in the guideline manuscript and to support drafting of recommendations.

3.6 Develop an evidence-to-recommendations table

Recommendations are formulated using the GRADE approach and are synthesized using an evidence-to-recommendations table. Under the GRADE process, recommendations are made by synthesizing information about the quality of evidence, balance of benefits and harms, values and preferences, and resource implications. This information comes from the systematic review as well as the review of review of harms and the narrative reviews for contextual questions. The quality of evidence is separate from the strength of recommendation. The quality of evidence is derived from the main systematic review while the strength of the recommendation is a reflection of not only the quality of evidence, but also values and preferences, resource implications and balance of benefits and harms.

The evidence-to-recommendations table is typically completed by the guideline lead. The coordinator acts in a support role to provide the guideline lead with the necessary data and literature, as well as any additional support needed.

Sample evidence-to-recommendations table (for PPIs):[13]

Does deprescribing PPIs (dose reduction, on-demand use, abrupt discontinuation, stepping down to H2RA therapy) compared with continuous PPI use result in benefits or harms for adults > 18 y (excluding those with history of bleeding ulcer, Barrett esophagus, and severe esophagitis grade C and D) in primary care and long-term care settings?

Decision Domain	Summary of Reason for Decision	Subdomains Influencing Decision
QoE: Is there high- or moderate-quality evidence Yes ☐ No ☒ (See references 1–16 in the evidence reviews at **CFPlus***)	The QoE for symptom relapse with deprescribing is low • Low-dose PPIs did not lead to significantly greater relapses than standard-dose PPIs did (RR = 1.16, 95% CI 0.93 to 1.44); on-demand PPI use and step down to an H2RA increased risk of symptom relapse compared with continuous PPI use (RR = 1.71, 95% CI 1.31 to 2.23, and RR = 1.92, 95% CI 1.44 to 2.58, respectively)	QoE for benefits with on-demand use: moderate • Lower pill burden: 3.5 fewer pills per week (95% CI −4.89 to −2.18)
Balance of benefits and harms: Is there certainty that the benefits outweigh the harms? Yes ☒ No ☐ (See the description of harms and references 17–20 in the evidence reviews at **CFPlus***)	Our systematic review showed that low-dose PPIs did not lead to a significantly higher GI relapse rate compared with standard doses. On-demand PPI use reduced pill burden. Cost, rare PPI side effects, and drug interactions were noted as potential concerns for continuous PPI use. Low-dose PPIs were thus considered to clearly have greater benefits than harms. On-demand PPI use and a step-down approach to H2RAs were also noted to have benefits over harms, but this was not as certain as the other deprescribing approach	Is the baseline risk for benefit similar across subgroups? Yes ☒ No ☐ • No evidence that benefits are different in subgroups Should there be separate recommendations for subgroups based on risk levels? Yes ☐ No ☒ • No evidence of benefit for any risk level Is the baseline risk for harm similar across subgroups? Yes ☒ No ☐ • No evidence that harms would be different for subgroups Should there be separate recommendations for subgroups based on harms? Yes ☐ No ☒ • No evidence for harms in subgroups
Values and preferences: Is there confidence in the estimate of relative importance of outcomes and patient preferences? Yes ☐ No ☒ (See references 1–3 and 21–25 in the evidence reviews at **CFPlus***)	In semistructured interviews patients reported that they believed PPIs were effective for preventing GI symptoms. However, it was also noted that most patients with GERD do not take their PPIs on a regular basis, and this has led to on-demand PPI research. Dose-lowering studies did not report patient satisfaction, while on-demand studies did not provide clear evidence on patient satisfaction	*Perspective taken*: the guideline group put high value on the lack of evidence of serious harms of deprescribing and on the reduction of medications and related harms and medication costs. Less value was placed on lack of information to determine the variability of patient values and preferences on different deprescribing approaches *Source of values and preferences:* semistructured interviews and other qualitative studies *Source of variability, if any:* variability difficult to estimateMethod for determining values satisfactory for this recommendation? Yes ☒ No ☐ • Clear preference to use PPIs to prevent GERD, but also evidence for on-demand and other reduced-dose use All critical outcomes measured? Yes ☒ No ☐ • More information on the various describing approaches would be helpful, but available evidence was clear

Resource implications: Are the resources worth the expected net benefit? Yes ☒ No ☐ (See references 19 and 26–39 in the evidence reviews at **CFPlus***)	In Canada, PPI use accounts for a high proportion of public drug program spending ($249.6 million in 2013). The recommended treatment duration for GERD, the most common GI symptom, is 4 wk; thus much of this PPI use is inappropriate. Several studies have demonstrated interventions to reduce PPIs are feasible. On-demand trials led to reduced pill burden. The cost of stopping PPIs, however, should be balanced against possible increased visits to physicians. Cost-effectiveness analyses were not available	*Feasibility*: Is this intervention generally available? Yes ☒ No ☐ *Opportunity cost*: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☒ No ☐ • The budget for PPIs is $69 million, and inappropriate PPI use is a considerable problem in adults and the elderly Is there a lot of variability in resource requirements across settings? Yes ☐ No ☒ • Deprescribing guidelines and implementation were considered to have relatively low resource requirements and to be feasible in primary care and long-term care
Strength of main recommendation: strong	Based on the lack of evidence of harm, the evidence for benefits of reducing inappropriate PPI use, the societal cost of inappropriate PPI use, and the feasibility of this intervention in primary care and long-term care	
Remarks and values and preference statement	The strong recommendation refers to low-dose or on-demand (as needed) PPI use. The weak recommendation refers to stepping down to H2RA therapy as a deprescribing approach. These recommendations place high value on zero to minimal clinical risk of deprescribing and on the inappropriate use of PPIs and resources, given the high cost associated with long-term PPI use, and some value on the potential harms and remote side effects (eg, pneumonia, diarrhea, *Clostridium difficile*, osteoporosis)	

GERD—gastroesophageal reflux disease, GI—gastrointestinal, H2RA—histamine-2 receptor antagonist, PPI—proton pump inhibitor, QoE—quality of evidence, RR—relative risk.

3.6.1 Become familiar with GRADE evidence-to-recommendations process

Consult the GRADE website (gradeworkinggroup.org) and relevant literature[5,14] to become familiar with the GRADE process of going from evidence to recommendations. Similar to the GRADE assessment, the coordinator may not be involved in synthesizing the recommendations but should be familiar with the methodology to be able to provide support.

3.6.2 Compile required evidence for GDT members involved in synthesizing recommendations

Compile the following information for the GDT member who is formulating recommendations: summary of findings and quality of evidence tables from GRADE assessment; section on harms (and benefits) of continued use of the drug/drug class; section on values and preferences of deprescribing of the drug/drug class, and section on resource implications for continuing or deprescribing the drug/drug class. This individual should also be sent the evidence-to-recommendations table template to formulate the recommendations.

3.6.3 Complete the evidence-to-recommendations table and draft recommendations

The GDT member should complete the evidence-to-recommendations table and formulate draft recommendations for voting by the GDT. The coordinator may assist the GDT member as needed throughout this process.

3.7 Draft recommendations and conduct GDT voting

Once the recommendations have been drafted by the guideline lead or responsible GDT member, the team needs to vote on, review and discuss the recommendations. The voting and feedback stage is intended to allow GDT members to voice any concerns about the recommendations, make any suggestions and have a discussion about how the recommendations are taking shape. It is important to determine how the group feels about the quality of evidence and strength of the recommendations, as well as the wording.

3.7.1 Organize voting on recommendations

Set up a meeting for voting on recommendations or decide on an alternate method of voting. The coordinator can discuss with the guideline lead and other GDT members how voting should take place (e.g., an in-person meeting, teleconference or email, perhaps via online survey tools). The method of voting may be influenced by GDT availability and budget factors.

3.7.2 Compile information to provide to GDT

Provide the GDT with evidence and rationale for the recommendations. The GDT should be provided with the summary of findings table, quality-of-evidence table and evidence-to-recommendations table, along with a draft of the recommendations. This should be distributed by email in advance of a face-to-face meeting or teleconference, or can be provided by email for email voting.

3.7.3 Complete preliminary ("straw dog") voting to stimulate discussion

Carry out a "straw dog" vote, to gauge how GDT members feel about the recommendations. GDT members can vote either yes or no, and provide any feedback or raise any issues about the recommendations.

The first two guidelines used 80% as consensus and used a blinded voting policy; however, this is not always necessary, as long as the method is clearly stated in the guideline itself.

The coordinator should send out an email outlining the procedures for voting (blinding versus unblinded; voting via email, at a teleconference or in-person meeting; level of consensus). The vote will then take place according to the pre-specified method of voting. The guideline coordinator is responsible for keeping track of votes.

Sample email for "straw dog" voting:

Hello Everyone,

We have been working furiously on our guideline content over the past weeks. Below are the draft recommendations provided to you for a straw-dog vote, and also to get your feedback and comments. I have attached several documents that will allow you to see the evidence behind the recommendations: (1) evidence profiles (summary of findings table and quality of evidence table), (2) GRADE evidence-to-recommendations table.

Instructions

Please email me back directly with a provisional YES or NO to these recommendations, and with any comments or feedback about the recommendations. Please respond within 48 hours. We would like to set up a call next week to discuss the recommendations and evidence. I will send out a poll for this. If we can't arrange a group call, then we can have individual calls with those who would like to discuss.

Best Regards,

3.7.4 Facilitate feedback and comments

The GDT can then discuss issues surrounding recommendations, and provide any feedback or comments. Again, this can be done via email exchanges, teleconference or an in-person meeting (typically the same meeting that voting took place at, but can be a separate meeting if necessary). The coordinator should compile the feedback and comments on the recommendations.

3.7.5 Revise recommendations based on feedback

The guideline coordinator works with the guideline lead to incorporate feedback and comments into revised recommendations. The recommendations are then updated.

3.7.6 Distribute revised recommendations

The revised recommendations should be circulated to the GDT for final approval. This can ideally be done using email, though if the guideline lead feels it is necessary another phone or in-person meeting/discussion may be required. After this round of reviews, the recommendations are finalized. Another final vote can then take place (yes/no) via email with 80% agreement indicating consensus. Steps 3.7.5 and 3.7.6 may need to be repeated depending on voting and feedback from the GDT.

3.8 Compile evidence, additional information and recommendations into guideline draft

3.8.1. Guideline content and structure

TIP

Review the clinical considerations sections of the published guidelines for ideas on what information might be needed to inform health care provider and patient decision-making.

All sections are incorporated into a guideline manuscript following the structure described below. The guideline coordinator can compile all of the information into a master document in collaboration with the guideline lead. The compiled document may be quite large to begin with, but is subsequently edited to reduce word count usually based on publication requirements, which may include moving sections to appendices.

Several examples of published deprescribing guidelines[12, 13,15-17] are available. Detailed information is generally included in appendices, while the main body of the manuscript serves as a brief summary of evidence and practical information for practicing clinicians. The general structure of previous guideline manuscripts is as follows:

Introduction

Include a brief description of the rationale or need for this deprescribing guideline as well as the scope of the issue. The target population of the guideline should also be described in this section.

Methods

The methods are briefly described and include a description of the GDT, GRADE process, deprescribing definitions for the drug/drug class and evidence to recommendations process. Cite the deprescribing guideline development methods paper[2], which readers can consult for more information on the process.

Recommendations
The criteria for considering deprescribing is described (e.g., for PPIs, patients who have completed a minimum four-week course of PPIs for upper GI symptoms or GERD, etc.), followed by the recommendations for deprescribing. The population of patients where deprescribing should *not* be done is also described in this section (e.g., patients with Barrett esophagus for PPIs). Any important clinical caveats can also be included (e.g., for BZRAs, duration and rate of tapering).

The rationale for the recommendation is summarized narratively below the recommendations. This information comes from the evidence-to-recommendations table and can include factors such as evidence behind deprescribing, patient preferences, resource implications, and benefits versus harms of medication continuation.

Clinical considerations
This section provides practical advice on deprescribing the medication(s). The section is synthesized based on evidence collected through the guideline development process and/or clinical experience. The sub-sections may vary based on the medication but have included topics such as how fast to taper, monitoring and factors that warrant continued use. The coordinator can work with the responsible authors and guideline lead to determine which sections will be included.

Clinical and stakeholder review
Include a brief summary of the clinical and stakeholder review. A list of bodies that endorsed the guideline is included in a table or figure.

Alignment with other guidelines
The content and recommendations for the deprescribing guideline can be put in the context of relevant treatment guidelines or evidence syntheses. For example, the PPI deprescribing guideline was discussed in the context of guidelines recommending a limited duration of PPI treatment in many patients.

Gaps in knowledge
This section highlights any notable gaps that were identified in the various evidence reviews. The section also makes recommendations for future studies.

Next steps
Most guidelines have included the following statement: “The deprescribing team will provide routine guideline updates as new evidence emerges that might change the recommendations. Prospective evaluation of the effects of adoption of this and other deprescribing guidelines will be part of a research strategy in the future.”

Conclusions
This is a high-level overview of the rationale for the guideline, evidence surrounding deprescribing and the potential impact of the guideline.

3.8.2 Process

As mentioned, the coordinator compiles all the individual sections into one large document, which is structured as outlined above. The coordinator can create the outline of the manuscript early in the guideline development process and insert sections as they are drafted. The individual authors for the sections typically send their respective sections in individual Word documents with relevant references listed.

After all sections are received, the coordinator and guideline lead can begin editing the document for continuity and clarity, and assigning content to appendices. Several rounds of revisions may be required before a final version is ready.

Once a suitable draft version is ready, the master document can then be sent out for rounds of reviews by the entire GDT. Several rounds may be required.

TIP

The manuscript format may change depending on the target journal.
See Section 5.2: Publish the guideline.

Section 4: Conducting clinical and stakeholder reviews

This section of the manual outlines steps to conduct and respond to clinical and stakeholder reviews. Review is a necessary component of producing a high quality evidence-based guideline. The draft guideline can be circulated to selected reviewers, and, if possible, piloted in practice sites to gain implementation experience. Stakeholder review, with potential endorsement, follows completion of the clinical review process, and is valuable to add credibility and promote guideline use.

Main Steps:

4.1 The AGREE II tool

4.2 Clinical review

4.3 Stakeholder review

4.1 The AGREE II tool[18]

The guideline review processes are guided by the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument. The AGREE II tool assesses methodological rigour and transparency within the guideline and within its development (www.agreetrust.org/about-the-agree-enterprise/introduction-to-agree-ii/). The instrument is both valid and reliable and is comprised of 23 items, though we have used the shorter five-item version in the past (see the sample AGREE II tool).

Sample AGREE II tool:

If you are not familiar with the tool or the process, find more information on how to use AGREE II here: www.agreetrust.org/resource-centre/agree-ii-grs-instrument/ This includes training on guideline development and the use of AGREE II: www.agreetrust.org/resource-centre/agree-ii-training-tools/ Note that these training exercises pertain to a 23-item AGREE II tool, and we are using the shorter five-item AGREE II global rating scale.

AGREE II-Global Rating Scale (AGREE II-GRS)

Instrument Instructions

The AGREE II-GRS Instrument consists of five items assessing how well the guideline is reported. The AGREE II-GRS is a reasonable guideline assessment tool alternative to, AGREE II, especially when time and resources are limited.

Table 1 provides information about the contents in each item category.[18]

Element	Description
Process of Development	Rate the quality of the development process. Consider: Were the appropriate stakeholders involved in the development of the guideline? Was the evidentiary base developed systematically? Were recommendations consistent with the literature? Was there consideration of alternatives, health benefits, harms, risks, and costs?
Presentation Style	Rate the quality of the guideline presentation style. Consider: Was the guideline well organized? Were the recommendations easy to find?
Completeness of Reporting	Rate the quality of reporting. Consider: 1) The transparency and reproducibility of the guideline development process. 2) The completeness of information to inform decision making.
Clinical Validity	Rate the quality of the guideline recommendations. Consider: Are the recommendations clinically sound? Are the recommendations appropriate for the intended patients?
Overall Quality	Rate the overall quality of the guideline. Consider: Your response to the above four items.

AGREE II-Global Rating Scale (AGREE II-GRS) Instrument[18]

Instructions: For each item, please choose the response on the seven-point scale that best characterizes the clinical practice guideline.

Item	Description	Lowest Quality (1) (2) (3) (4) (5) (6) Highest Quality (7)
1. Rate the overall quality of the guideline development methods	Consider: Were the appropriate stakeholders involved in the development of the guideline? Was the evidentiary base developed systematically? Were recommendations consistent with the literature?	☐ ☐ ☐ ☐ ☐ ☐ ☐
2. Rate the overall quality of the guideline presentation	Consider: Was the guideline well organized? Were the recommendations easy to find?	☐ ☐ ☐ ☐ ☐ ☐ ☐
3. Rate the completeness of reporting	Consider: Was the guideline development process transparent and reproducible? How complete was the information to inform decision making?	☐ ☐ ☐ ☐ ☐ ☐ ☐
4. Rate the overall quality of the guideline recommendations	Consider: Are the recommendations clinically sound? Are the recommendations appropriate for the intended patients?	☐ ☐ ☐ ☐ ☐ ☐ ☐
5. Rate the overall quality of the guideline		☐ ☐ ☐ ☐ ☐ ☐ ☐

4.2 Clinical review

4.2.1 Identify clinical reviewers

Ideally, the clinical reviewers should be members from each professional group that will use the guideline (most likely family physicians, pharmacists, nurse practitioners, and possibly a long-term care physician or a pediatrician depending on the target population). The clinical reviewers should be informed of the topic and intended audience of the guideline. All comments made by reviewers must be responded to; therefore, it is advised to keep the number of reviewers manageable.

Clinical reviewers may be sought out by GDT members based on their expertise, or they may volunteer to review.

4.2.2 Conduct clinical review

Once identified, the clinical reviewers should be formally invited via email.

TIP

To avoid delays, identify and recruit clinical reviewers about two months in advance of when they can expect to conduct their review. We found two to four clinical reviewers were sufficient.

Sample clinical reviewer request:

Hello _____,

My name is _____. Our team is developing a benzodiazepine receptor agonist (BZRA) deprescribing guideline and I am writing to ask if you are willing to be a clinical reviewer for this guideline. You have been identified as a potential reviewer because your…

The guideline will be available for review in mid-late January and we are anticipating an approximately two-week turn around period. Please review the following and let us know if you believe you can meet the time commitment.

We would send you a draft guideline in mid-late **January and plan for feedback by end of January or early February**. The document will be between five and eight pages long and there will also be a one-page algorithm that will act as a clinical tool to be used in practice. We ask that the AGREE II 5-item Global Rating Scale be used to complete the review. I have attached a copy for your information. If you are not familiar with the tool or the process, more information on how to use AGREE II can be found here: www.agreetrust.org/resource-centre/agree-ii-grs-instrument/ This includes training on guideline development and the use of AGREE II: www.agreetrust.org/resource-centre/agree-ii-training-tools/ Note that these training exercises pertain to a 2- item AGREE II tool, and we are using the shorter five-item AGREE II global rating scale. If you have questions about the process after reviewing all of the training materials, we can help answer them.

Please let us know if you agree to participate as a clinical reviewer of the BZRA Deprescribing Guideline.

Thank you for your interest in the project and we hope that the timing of this request works for you,

With the invitation, information on AGREE II should also be provided. Upon agreement to review, all clinical reviewers must sign a confidentiality form before receiving the guideline (sent via email). The guideline should be sent in a PDF and watermarked CONFIDENTIAL. You may instruct reviewers on the best way to provide comments that are suitable for you and your team. We have typically instructed reviewers to provide comments directly on the PDF or in the body of an email, whichever way was most convenient for them to facilitate a prompt review.

Sample clinical reviewer confidentiality agreement:

Deprescribing Guideline Confidentiality Agreement

I agree that I will protect the Deprescribing Guideline and not distribute it to any other person(s) within or not within my organization.

I agree that all information relating to the Deprescribing Guideline will be kept confidential.

I will use the information accessed only as needed to do my job.

In accessing, using, storing and disposing any of the guideline information, I will follow the correct procedure (such as using passwords to protect documents and shredding confidential papers before throwing them away).

I will not divulge confidential information nor allow access by unauthorized persons.

By signing this document, I agree that I have read, understand and will comply with this agreement:

Name: _____

Signature: _____ Date: _____

4.2.3 Respond to clinical review

A face-to-face meeting with the research coordinator and guideline lead is necessary to respond to general comments. The GDT will also be needed to respond to more specific items relating to the content for which they were responsible for. Emails should be sent individually, or telephone meetings should be arranged to discuss comments with the most pertinent GDT member. The completed clinical review response table should then be sent to all GDT members, and upon approval, sent back to the reviewers in order to thank them for their review and to show how their comments have been addressed. See Appendix A for the full table.

Sample clinical review response table (condensed from antihyperglycemic deprescribing guidelines):

Comment	Response
Reviewer 1 (Pharmacist)	
1. pg 2: - individualizing therapy, including targets, to goals of care…	Thank you for your comment, we have made the suggested change.
2. - We suggest deprescribing of antihyperglycemic drugs when individualized targets have been relaxed, particularly if …	Thank you. We have not made this particular wording change because our recommendation relates to deprescribing medications known to contribute to hypoglycemia for those at risk of hypoglycemia, regardless of individualized targets.
3. pg 3 - might diabetes educators be a target audience? They often contribute and drive the approach to glycemic control	This is a good observation and we have added certified diabetes educators as another target audience for the guideline.
4. pg 6 - first study - just wondering if 87% were just switched to glipizide, is this really deprescribing? I do not note any benefit or harm.	As noted in Box 2, on page 5 of the guideline, our definition of Deprescribingincludes prescription substitution to reduce medication risk, (which would include switching from glyburide to glipizide).
5. - second study - "The deprescribing group had a non-significant lower all-cause mortality risk; RR: 0.74 (95% CI: 0.29, 1.87)." I have a problem with saying they had a non-significant lower risk when the CI is so wide. You could say that mortality was not increased and provide the statistics.	Thanks for this suggestion. You raise a valid point given the imprecision of this measurement. We have changed the wording to read: "There was no significant difference in mortality between the deprescribing group and continuation group (RR 0.74, 95% CI 0.29 to 1.87)"

4.3 Stakeholder review

4.3.1 Identify and invite stakeholders to review and potentially endorse the guideline

Stakeholders (relevant professional groups and organizations) should be identified early on as groups that could endorse the guideline. Such groups should be pertinent to the guideline being developed (e.g., organizations or professional groups for gastroenterologists for the PPI guideline). Such groups can be invited by mail/email through contacts for each group (found on their websites, or suggested by the GDT) to review the guideline and consider endorsing it. A stakeholder communication table should be created to document and track stakeholder responses (see sample below). Once individuals representing these groups, or review committee members have agreed to participate, they can be send confidentiality forms to sign.

TIP

To avoid delays, identify stakeholders about two months in advance of when they can expect to conduct their review. We found it sometimes took several communications to gain agreement, then additional time to collect signed confidentiality forms before the guideline could be sent for review. Because of the sometimes large number of stakeholders, a tracking table was absolutely mandatory.

Stakeholders asked to review and potentially endorse the previously published deprescribing guidelines include:

- College of Family Physicians of Canada
- Canadian Nurses Association

  Canadian Pharmacists Association
- Canadian Association of Gastroenterology
- Ontario Pharmacists Association
- RxFiles

A sample email and letter attachment sent to stakeholders requesting their review and subsequent endorsement during the stakeholder review process follows.

Sample endorsement request email:

Dear _____,

My name is _____ (GDT lead). Introduce self.

I am writing you with an invitation to review and/or endorse our Deprescribing Guideline on _____.

A formal letter of invitation is attached and we would appreciate a reply by ___ to indicate the interest of your organization in reviewing and/or endorsing the guideline throughout ___. Once we know of your interest, we will be in touch with confidentiality forms, and then a copy of the guideline for review.

If you have any questions, please contact myself or the ____ deprescribing guideline coordinator _____ .

Sincerely,

GDT lead

Sample endorsement request letter:

Attn: _____

Stakeholder address

Re: Deprescribing Guideline Endorsement

Dear _____,

I would like to invite your organization to consider reviewing and/or endorsing a Deprescribing Guideline for (target drug class).

Deprescribing involves reducing doses or discontinuing medications that may be causing harm or offering little benefit. Our project will systematically develop three such guidelines and evaluate their implementation in practice with older adults.

We are working closely with a number of experts to develop this guideline, which focuses on deprescribing_____(drug class)_____. We are using a systematic evidence-based approach based on GRADE and AGREE II to develop the guidelines.

Our GDT includes ___(team member names and expertise)___ as members.

At this time, we are asking whether your organization/group would be interested in assisting with the review process (using a standardized template) and/or be willing to endorse the final _____(drug class)_____ deprescribing guideline during _____(date)_____. Also, we would appreciate your recommendation of a key contact person within your organization with whom/who we can correspond in future.

If you have any questions, I would welcome the opportunity to discuss the project in-person or by telephone, whichever is most convenient for you. Please contact me via at the coordinates below.

On behalf of our research team, I look forward to your reply.

Sincerely,

Sample stakeholder tracking table:

Overall Status (insert date):
X/10 Finished review
X/10 Received guideline for review
X/10 Awaiting confidentiality agreement (have not sent guideline)
Some stakeholders may require additional information before agreeing to review the guideline. Some common queries and example responses follow.

Org. #	Association/ organization	Initial contact person	New contact person	Initial email	Email exchanges	Review/ endorser email sent	Confidentiality form received	Anticipated timeline	Review completed
1.									
2.									
3.									
4.									
5.									
6.									
7.									
8.									
9.									
10.									
11.									

Sample questions from stakeholders prior to review (example from antipsychotic deprescribing guideline):[15]

Information needed	Information provided to stakeholder
Name of product or document	Evidence-based Clinical Practice Guideline for Deprescribing Antipsychotics
Source of development	Bruyère Research Institute, Ottawa ON, along with GDT members at various institutions (see guideline title page for full list)
Name(s) of person(s) in the organization responsible for development	Lise M. Bjerre (guideline lead) with nine other GDT members
Is this the final draft?	Pending comments from CFPC and other stakeholder reviews
Four complete copies of the product enclosed with references, addenda, etc.	One electronic copy
Further information about the project: • Proposed release date, launch, distribution • Promotion - is the CFPC invited to participate? • Dissemination (e.g., advertising in *Canadian Family Physician*) • Available in both official languages • Available through media (print, internet, etc.) • Print run (number of copies, cost per copy, etc.)	 Guideline will be submitted for publication immediately following review/endorsement process Yes We don't have any funding to support advertising, but once published, CFPC would be welcome to advertise in an appropriate manner The algorithm will be available in English and French. The guideline will be published in English. Planning to submit in an Open Access journal, so the guideline should be available freely online. Algorithm will also be posted on the Deprescribing website
Are the expectations of both parties clear? • Use of the CFPC name and visual identify • Collaboration for launch and/or distribution • Type of association • Financial or staff support from the CFPC/for the CFPC	 The guideline will indicate whether endorsed by CFPC. Decision to use visual logo may depend on journal. The logo will not be on the algorithm itself due to space issues but CFPC name (and possibly logo) could be on the website page with the algorithm No expectations Looking for endorsement only No expectations
Does the requester understand the CFPC endorsement process? • Endorsement based on reviews of three members and approval of Executive Committee • No advance guarantee that the product/document will be endorsed • Limits of endorsement (e.g., application to reviewed product only) • Time factor (6 to 10 weeks) • Executive Committee's decision final	 Yes Yes Yes We have communicated that six weeks is the goal Yes

4.3.2 Conduct stakeholder review and request endorsement

Once a draft of the guideline is available post-clinical review, this next 'near-final' watermarked "confidential" version can be sent to the groups that have agreed to review and potentially endorse the guideline. Generally, a member or committee chosen by the organization (based on expertise) will review the guideline on behalf of the organization. AGREE II may be used in the review process as it was with clinical reviewers.

Most organizations will nominate an expert from their association to review. For the stakeholder review, the coordinator may have to fill out a form or a similar document requesting review. If the association decides to endorse the guideline, they then send documentation such as a letter or email outlining their endorsement. This document can then be saved with the project files, and the organization can be included in the guideline manuscript as having endorsed the guideline.

TIP

Some organizations requested their logos be added to the guideline algorithm however this made the algorithms look cluttered, Instead, all organizations endorsing the guideline are included in the manuscript and their logos included in presentations and other tools related to the guideline.

Section 5: Facilitating knowledge mobilization

Main Steps:

5.1 Develop an algorithm

5.2 Publish the guideline

5.3 Disseminate deprescribing guidelines and support resources to various user groups

5.1 Develop an algorithm

An algorithm is a decision support tool, summarizing the specific guideline content and aiding the health care provider in deciding when and how to use the recommendations. Start by reviewing each of the available deprescribing algorithms for similarities and differences (see Appendices B-F). Compare also to their corresponding published guideline to see how the guideline information is summarized. [12, 13,15-17]

5.1.1 Design a template

The algorithm template should consist of the front and back of one sheet of paper. The front page contains the decision support guidance, while the reverse includes additional information such as drugs and doses available, patient engagement advice, side effects and non-pharmaceutical approaches to symptom management. Both pages should contain a creative commons citation (see the available algorithms in Appendices B-F for wording and citation recommendations).

5.1.2 Complete the flow chart for the front page

The decision as to whether to deprescribe may depend on the reason for medication use, and/or risks of its use. The first step is often to identify why the patient is taking a medication. Patients who should continue to take the medication (because of clear evidence for benefit of continued use) should be clearly identified. Patients who are candidates for deprescribing should also be identified based on the evidence reviewed in the guideline. The recommendations should be worded as closely as possible to what is contained in the full guideline. When possible, add numbers-needed-to-harm (e.g., would experience adverse drug withdrawal events from deprescribing). Advice regarding dose reduction processes can be gleaned from deprescribing studies and also from the clinical expertise of the GDT and reviewers. Information should be consistent with the guideline contents. Similarly, monitoring advice can be gleaned from deprescribing studies and the clinical expertise of the GDT and reviewers. Consider how monitoring approaches may differ depending on patient preferences and/or clinical status (e.g., for verbal versus non-verbal patients). Next, advice should be provided regarding managing symptom return including when additional testing is recommended (as per the guideline).

There are slight variations between the different algorithms. For example, the BZRA deprescribing algorithm contains a patient engagement section before to the deprescribing recommendation (see Appendix E). This was felt to be important to some GDT members and reviewers who had had experience with patients trying to taper off BZRA; the feeling was that no recommendation to reduce a BZRA should be made until the patient was engaged in the discussion. For other medication classes, there was the feeling that decisions about making deprescribing recommendations could be made and then the patient approached for agreement. Patient values and preferences should always be incorporated into decisions surrounding continuing or deprescribing a medication. Most of the algorithms begin with asking “why is the patient taking the drug,” because the reason for the drug’s use often dictates whether it is still required. However, for antihyperglycemics, this was not relevant; they were always prescribed for diabetes. In this algorithm, the more important considerations included risk factors the patient might have for hypoglycemia, whether they were experiencing or at risk of other adverse effects, or there was uncertainty of clinical benefit (see Appendix B).

5.1.3 Add other relevant information for the back page

Typically, include the following information on the back of each algorithm:

- Relevant drugs and doses available in Canada
- Recommendations for patient engagement
- More detailed advice on tapering doses (including whether or not there was evidence to support one tapering strategy over another)
- Non-pharmaceutical management strategies

The antihyperglycemic algorithm contains additional information regarding medications that affect blood glucose, as well as relevant drug interactions as they were pertinent to decision-making about deprescribing (see Appendix B). Again, any information on the back of the algorithm must be consistent with content in the guideline.

TIP

A good rule of thumb is there should be no algorithm content that is not contained in the guideline itself.

5.1.4 Develop other resources for health care providers and patients

The decision support algorithm is the main tool that can support health care providers in making decisions related to deprescribing. With additional funding, you could consider developing patient information pamphlets, infographics and Youtube videos demonstrating clinical examples of using the guidelines. Development of these tools is beyond the scope of this manual but examples can be found in the patient resource section of our website (https://deprescribing.org/resources/deprescribing-information-pamphlets/) and the Youtube channel (www.youtube.com/channel/UCwqOu26_nAMmUyb3fyKxBbw).

5.1.5 Translation

If requests for translation of the algorithm are made, follow the translation policy outlined below.[19]

1. Contact us and let us know that you would like to translate the algorithm. You can do this by e-mailing deprescribing@bruyere.org.
2. We will respond to your request usually in less than seven days.
3. If you have not already done so, identify two professional translators. One will do the forward translation, and the other will do the backward translation. Note: The translator who is doing the backward translation should not be shown our original English language materials.
4. Have one translator conduct the forward translation.
5. Have the second translator do the backward translation into English.
6. Send the backward translation to us so we can verify its quality. We will provide our comments and revisions.
7. Make the necessary revisions.
8. Provide us with copies of your final materials.
9. Begin to use your translated algorithms.

5.2 Publish the guideline

The first four guidelines are published in Canadian Family Physician.[12, 13,15-17] A fifth guideline, developed through a partnership with Australian NHMRC Partnership Centre, has been published on the University of Sydney website.[17]

In order to write the content for the publishable guideline as efficiently as possible, identify appropriate target journals early on in the process. Consider the target audience, receptivity to guideline publication and related costs. Contact the editor early on to discuss interest and preferred format. Share other published deprescribing guidelines as examples of the method you are following. Adhere to their recommendations for formatting, including what information they want as appendices or online resources. Obtain permission to share the algorithm and supporting resources freely prior to guideline publication. Publications can remain "in press" for several months and you want to be able to have people use the algorithm while you wait for final publication. Once the guideline is published, update the citation on the algorithm (and other tools, if any) with the final version.

Credibility is added to a guideline publication when the GDT members are described in terms of their roles, expertise and conflicts of interest. The following table provides an example of how such information can be included.

Sample author expertise and responsibilities table that will be included in the publication (from the antihyperglycemc guidelines):[12]

Guideline Member	Expertise	Guideline Responsibilities	Conflict(s) of Interest
Barbara Farrell (Guideline lead)	Pharmacist (Geriatric Day Hospital, lead on the Deprescribing guidelines in the elderly project)	• Introduction • Recommendations • Gaps in knowledge • Conclusion	Research funding received for the purposes of developing this guideline
Manon Bouchard	Nurse practitioner (Family Health Team)	• Resource implications • Patient values and preferences	None declared
Heather Lochnan	Endocrinologist	• Clinical considerations • Other guidelines	Member of Canadian Diabetes Association; has received funding and participated in multi-centre diabetes clinical trials with sponsorship from pharmaceutical companies that produce agents for management of diabetes
Lisa McCarthy	Pharmacist (community and primary care settings)	• Review of reviews of harms	Former member of the Canadian Diabetes Association, Diabetes Educator Section
Carlos Rojas-Fernandez	Pharmacist (geriatrics, primary and long-term care settings)	• Clinical considerations • Other guidelines	None declared
Salima Shamji	Family Physician (care of the elderly)	• Review of reviews of harms	None declared
Wade Thompson	Pharmacist (Long-term care)	• Summary of findings and certainty of evidence • GRADE review • Patient values and preferences • Clinical considerations	None declared
Ross Upshur	Family physician	• Patient values and preferences	None declared
Vivian Welch	Clinical epidemiology methodologist	• Summary of findings and certainty of evidence • GRADE review • Gaps in knowledge	None declared

TIP

Because the guideline will have already had both extensive clinical and stakeholder review, it's unlikely that the publication peer review process will identify serious concerns. Refer back to the response tables you developed for clinical and stakeholder comments to see if you can use previous responses should any concerns arise during the peer review process.

5.3 Disseminate deprescribing guidelines and support resources to various user groups

Once you have developed your algorithm and guideline support resources, and have submitted your guideline for publication, efforts should be made to maximize the spread of the guideline and support tools to various users. A multi-pronged approach to dissemination should be used to achieve this objective. Websites can be used to house available resources. Social media platforms (e.g., Twitter, Facebook) can be used to target and notify individuals or groups when guidelines are published and when new tools become available. Conferences and symposiums for researchers or health care providers can be an effective way to notify these users that a new deprescribing guideline is available for use and/or to be formally evaluated in practice. Smaller, local health and wellness fairs or other community events for members of the public can serve as optimal venues to build awareness about the concept of deprescribing and share the deprescribing guideline support tools available for patients. Identifying key individuals in the community you are trying to reach (e.g., physician in a medical clinic, pharmacist in a community pharmacy, member of a long-term care home family or resident council, volunteer at senior support centre) and engaging them to be a "deprescribing champion" can also assist you with spreading information about your guideline and the availability of deprescribing support resources.

TIP

Take advantage of your connection with the Bruyere Deprescribing Guidelines Research Program to share your guideline and algorithm through their website and social media.

Conclusion

Thank you for your interest in developing a deprescribing guideline. This user guide is a work-in-progress. Please submit any suggestions, feedback or additional examples to deprescribing@bruyere.org

References

1. Schünemann H, Wiercioch W, Etxeandia I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *CMAJ*. 2014;186(3):E123–42.

2. Farrell B, Pottie K, Rojas-Fernandez C, et al. Methodology for developing deprescribing guidelines: using evidence and GRADE to guide recommendations for deprescribing. PLoS One. 2016;11(8):e0161248.

3. Higgins JPT, Green S, eds.. *Cochrane Handbook of Systematic Reviews of Interventions* Version 5.1.0 [Updated March 2011]. The Cochrane Collaboration, 2011. Available: http://handbook-5-1.cochrane.org/ (accessed Feb. 28, 2018).

4. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339(1):b2700.

5. Guyatt G, Oxman A, Akl E, Al. E. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383–94.

6. CADTH. PRESS peer review of electronic search strategies.
Available: www.cadth.ca/resources/finding-evidence/press (accessed Feb. 19, 2018).

7. Shea B, Grimshaw J, Wells G, Al. E. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* 2007;7(10).

8. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ [Internet]. 2015 Jan 2 [cited 2016 Nov 2];349:g7647. Available: www.ncbi.nlm.nih.gov/pubmed/25555855 (accessed Feb. 28,2018).

9. Black C, Thompson W, Lochnan H, McCarthy L, Rojas-Fernandes C, Shamji S, Upshur R, Welch V, Farrell B. Benefits and harms of deprescribing versus continuing antihyperglycemics for treatment of Type 2 Diabetes Mellitus: a systematic review protocol. PROSPERO 2015:CRD42015025727. Available: www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015025727
(accessed Feb. 25, 2018).

10. Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. *Syst Rev* 2016 Nov 14;5(1):190.

11. Smith V, Devane D, Begley CM, Clarke M. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. *BMC Med Res Methodol*. 2011;11(1):15. pmid:21291558.

12. Farrell B, Black C, Thompson W, McCarthy L, Rojas-Fernandes C, Lochnan H, Shamji S, Upshur R, Bouchard M, Welch V. Deprescribing antihyperglycemic agents in older persons. *Can Fam Phys* Nov. 2017, 63(11)832-43. Available: www.cfp.ca/content/63/11/832 (accessed Feb. 19, 2018).

13. Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ, Rojas-Fernandez C, Walsh K, Welch V, Moayyedi, P. Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. *Can Fam Phys*, May 2017, 63(5):354–64.

14. Andrews J, Schünemann H, Oxman A, Al. E. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength.
J Clin Epidemiol. 2013;66(7):726–35.

15. Bjerre LM, Farrell B, Hogel M, Graham L, Lemay G, McCarthy L, Raman-Wilms L, Rojas-Fernandes C, Sinha S, Thompson W, Welch V, Wiens A. Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia. *Can Fam Phys* Jan. 2018, 64(1)17-27. Available: www.cfp.ca/content/64/1/17 (accessed Feb. 19, 2018).

16. Pottie K, Thompson W, Davies S, Grenier J, Sadowski C, Welch V, Holbrook A, Boyd C, Swenson JR, Ma A, Farrell B (2016). Evidence-based clinical practice guideline for deprescribing benzodiazepine receptor agonists. Unpublished manuscript.

17. Reeve E, Farrell B, Thompson W, Herrmann N, Sketris I, Magin P, Chenoweth L, Gorman M, Quirke L, Bethune G, Forbes F, Hilmer *S. Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine*. Sydney: The University of Sydney; 2018. ISBN: 978-0-6482658-0-1 Available: http://sydney.edu.au/medicine/cdpc/documents/resources/deprescribing-guideline.pdf (accessed March 2, 2018).

18. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham I, Grimshaw J, Hanna SE. The global rating scale complements the AGREE II in advancing the quality of practice guidelines. *J Clin Epidemiol* 2012;65(5):526-34; doi: 10.1016/j.jclinepi.2011.10.008. Available: www.agreetrust.org/wp-content/uploads/2017/11/AGREE-GRS.pdf (accessed March 11, 2018).

19. Farrell B, Rojas-Fernandez C, Dolovich L. Deprescribing Guideline and Support Tool Translation Policy. 2015. Available: www.open-pharmacy-research.ca/evidence-based-ppi-deprescribing-algorithm/ (accessed March 7, 2018).

References

Appendix A: Clinical Review Response Table

Antihyperglycemic Clinical Reviewer Feedback - Compiled

Comment	Response
Reviewer 1 (Pharmacist)	
1. pg 2: - individualizing therapy, including targets, to goals of care…	Thank you for your comment, we have made the suggested change.
2. - We suggest deprescribing of antihyperglycemic drugs when individualized targets have been relaxed, particularly if …	Thank you. We have not made this particular wording change because our recommendation relates to deprescribing medications known to contribute to hypoglycemia for those at risk of hypoglycemia, regardless of individualized targets.
3. pg 3 - might diabetes educators be a target audience? they often contribute and drive the approach to glycemic control	This is a good observation and we have added certified diabetes educators as another target audience for the guideline.
4. pg 6 - first study - just wondering if 87% were just switched to glipizide, is this really deprescribing? I do not note any benefit or harm.	As noted in Box 2, on page 5 of the guideline, our definition of Deprescribing includes prescription substitution to reduce medication risk, (which would include switching from glyburide to glipizide).
5. - second study - "The deprescribing group had a non-significant lower all-cause mortality risk; RR: 0.74 (95% CI: 0.29, 1.87)." I have a problem with saying they had a non-significant lower risk when the CI is so wide. You could say that mortality was not increased and provide the statistics.	Thanks for this suggestion. You raise a valid point given the imprecision of this measurement. We have changed the wording to read: "There was no significant difference in mortality between the deprescribing group and continuation group (RR 0.74, 95% CI 0.29 to 1.87)"
6. - Overall, this systematic review suggests that it is probably not harmful… Could get rid of word "probably" since you are already using "suggests"	We have removed 'probably' from this statement.
7. pg 7 - …macrovascular complications (e.g. non-fatal myocardial infarction) in adults, over 5-10 years… could say 5-10+ years as evidence definitely leans towards a longer period	We have added the suggestion to the text to reflect the potential for reduction in risk to take longer than 10 years to be reflected.

8. regarding the empagliflozin study; it might be good to note that in addition to the benefits observed in the trial, there were also harms - Increased genital infections 6.4 vs 1.8% NNH=22, esp in women - 17 % discontinued due to adverse events related to empagliflozin - 25.4% discontinued study med (28% plasma glucose <3.9mmole/L) - Urosepsis 0.4 vs 0.1% - Genital infections (5 vs 1.5% in men; 10 vs 2.6 % in women) - Placebo group had more insulin & sulfonylurea use (? harmful) overall - I think that the benefits section is an important one to provide info on given the limited benefits seen, or in the case of ACCORD - an increase in all-cause mortality with the very aggressive tx group. Might be worth adding a note regarding ACCORD specifically as deprescribing is what would potentially save the life of a patient in the aggressive treatment arm of the ACCORD trial.	Thank-you for this comment. While we were in the process of modifying the empaglifozin section to refer to the related Harms section, the CDA guidelines provided an interim update on pharmacological management of Type 2 Diabetes that includes empaglifozin. We have modified this section to refer to the 2016 update. In addition, the harms of empagliflozin are outlined in the paragraph about sodium-glucose cotransporter 2 inhibitors (from systematic review) in the Harms section with odds ratios, and relative risks outlined in Appendix C. We have added the following to the description of the intensive control studies: "indeed, all-cause mortality was increased in the intensive glycemic control group."
9. pg 9 - …criteria state that glyburide should be avoided in older … Agree, but just of interest, the last I looked into it, all the data to suggest that gliclazide might be safer is from studies using the short acting whereas now we are using the once daily formulation. Since hypoglycemia risk was somewhat related to glyburide's long-action, this does provide for some interesting questioning around our general assumptions that gliclazide MR is also any safer.	The risk of hypoglycemia with different sulfonylureas has been added to the clinical considerations section (What deprescribing should happen) and Table 3. This includes referencing literature demonstrating lower risk with short-acting and long-acting formulations of gliclazide.
10. pg 10 - might it help to have some estimation of how common, uncommon or rare the harms are? Specifically the GI effects of acarbose are very common (likely >40% ?) wherease the bladder ca with TZDs, if it occurs, is much more rare.	Estimating the prevalence of side effects is very challenging as they are reported inconsistently, may vary with dose and arise from numerous different types of sources (controlled trials, product monographs, post-marketing surveillance). We therefore opted to summarize adverse effects as identified in systematic reviews of harm. This approach typically provides relative risks, and odds ratios that help identify increased risk of adverse effects with specific medications, but do not always provide estimates of prevalence. In terms of the example of acarbose, systematic review findings indicate a 15-30% incidence (stated in Appendix C). The following statement appears in the Harms section as well: "When weighing the risks and benefits of a particular medication, we encourage readers to consider the effect size for the increased risk in the context of how frequently the medication is used and the patient's baseline risk."

11. pg 11 - In summary, some older adults may prefer intensive glucose control, while others may prefer less intensive therapy. - Dr Victor Montori discusses some of this around the terminology that some may prefer "minimally disruptive therapy"	Minimally disruptive therapy is discussed on page 16 in reference to determining the need for continued use of antihyperglycemics – weighing benefits and harms.
12. pg 30 - Do the Canadian guidelines use some qualifiers for suitable targets (individualize; if can be achieved without hypoglycemia)	The qualifiers for individualized higher A1C targets from the CDA from Figure 1 have been added to Table 1
13. pg 32 - could add in something from the VA in the USA, as they are more lenient	Comparison of the VAMC guidelines with those synthesized by other expert groups doesn't provide a meaningful different set of parameters, and is less specific in some regards. In addition, the VAMC guidelines are presumably synthesized for a predominantly male population in a unique health care system which is very different from our primary care or long term care system in Canada, making generalization problematic.
14. General What about a comment on "self monitoring of blood glucose", or how often to check. This is also an area for potential deprescribing especially when individuals are not on insulin, and have relaxed targets.	This statement already appears in the Monitoring section of the Clinical Considerations: Once a patient's blood glucose is stable and hypoglycemia is no longer a risk or is significantly diminished, the frequency of blood glucose testing can be reduced or stopped in accordance with CADTH recommendations, which suggest regular blood glucose testing is not routinely required with antihyperglycemics except in circumstances of dose changes or concurrent illness
Reviewer 2 (Geriatrician)	
15. Thank you for allowing me to review the guideline. It is very well written and comprehensive. You are to be commended for your efforts and it should be published. My main concern is that there is a paucity of evidence on which to base a guideline, and the conclusions by their very nature must be speculative. While I agree with the general thrust, I find it difficult to think that you can make recommendations graded as strong given the evidence available. A more modest statement would be better. I have a few things for you to consider if you wish to make some revisions.	Thank-you. We agree that there is a paucity of evidence for deprescribing antihyperglycemics; we elaborate on this further in the "Knowledge gaps" section. The use of the rating "strong" for the recommendation incorporates the evidence for deprescribing, as well as the evidence for harm (ie. of hypoglycemia and other adverse effects), patient values and preferences, and resource implications as per the GRADE framework. Using this framework, the word "strong" implies that most patients would wish to follow the recommendation, and only a slight proportion would not. A "strong" recommendation can be based on low quality or low certainty evidence as is this case. If new, better evidence arises, this can shift the nature of the recommendation itself and our team will monitor for the publication of such new evidence.

16. You have quite clearly articulated the risks of low blood sugar in a frail population. It might also be worth mentioning how shockingly common tight control is in this frail population. I have attached a reference from Huang.	Thank you for the reference. We have included a brief note about how common tight control truly is in this population in the harms section and referred to the Huang article.
17. You have also clearly articulated that tight control is unlikely to have any significant benefit in a frail patient with a short life expectancy. However, I don't think you have given enough credence to the alternate hypothesis. By that I mean what are the short to medium term consequences of high blood sugar levels, which could include impacts on cognition and affect, infections etc? There is really no evidence to inform either hypothesis so they need to be given equal time. Someone needs to do a randomized controlled trial to determine the appropriate set point for this population	Thank-you for this comment. We have added further information about avoiding osmotic diuresis to the benefits section, and to the section on weighing benefits and harms. We have also indicated in the "Knowledge gaps" section that the impact of high blood glucose levels on cognition and infections are largely unknown and warrant further investigation to help identify evidence-informed treatment targets.
18. I have included a couple of references that support your contention as to why the elderly are more susceptible to hypoglycemia (Meneilly/Bremer).	These references were very helpful and were referred to in the hypoglycemia subsection of the harms section.
19. There is some data to suggest the sulfonlyureas are more likely than insulin to cause hypos when used with other agents. Not sure why, but its interesting. (Barnett)	We were unable to locate this information. A review authored by Barnett investigated hypoglycemia risk with various add-on therapy to insulin, but did not directly compare insulin to sulfonylureas. Our guideline coordinator has been in touch with the reviewer for a copy of the reference to which he refers.
20. Several of the guidelines you quote not only described relaxed targets for the frail, but also emphasize that you have a floor as well. In other words, don't ever go below a sugar of 6 or an A1C of 7.5 for the frail. You allude to this, but could emphasize it more strongly. I think it would be fair to say in table 2 under CDA that the A1C target should be less that 8.5, not to say avoid tight control	The following statement has been added to the paragraph on appropriate A1C and blood glucose targets: "Some guidelines recommend lower limits for A1C levels; these are noted in Table 2." We have not modified our recommendation due to the lack of specific evidence to support the variations in 'lower limit' recommendations. This could be re-evaluated in future. Table 2 has been changed to include the CDA target.
21. There is a recent reference from Munshi that you might find illuminating. I have attached it for your perusal.	Thank-you for this paper (ADA position statement on management of diabetes in LTC). It provides a very useful overview of interprofessional and patient-relevant management of diabetes in LTC. We have added a reference to it in the section about other guidelines.
Reviewer 3 (FHT Pharmacist)	

22. The size of the guideline development team was relatively small, this weakens the reliability of recommendations which are consensus/expert opinion-based it could be improved with endorsement by larger numbers/groups of endocrinologists, physicians, allied health professionals in relevant sectors (including palliative care, longterm care associations) and patients/ advocates on the committee with perspective/input on acceptability of guideline recommendations aside from published literature from patient surveys. For instance, the patient voice is now incorporated into CDA guidelines *"Inclusion and active participation of people with diabetes on the Expert Committee to ensure that their views and preferences informed the guideline development process and the recommendations."*	Thank-you for this comment. We included guideline team members representing medicine (family medicine, geriatrics, care of the elderly and endocrinology), nursing and pharmacy, as well as those with GRADE and Cochrane expertise. Several members had both primary care and long-term care experience. We have added to the guideline development team member table to more fully describe expertise and background of each member. Although we conducted a literature search for patient values/preferences, we agree that it would have been ideal to have included patient input regarding the recommendations. CDA has agreed to have their expert committee review the guideline and its recommendations as part of the stakeholder consultation process following the current clinical review process. In addition to five clinical reviewers (endocrinologist, geriatrician, pharmacists), the guideline will also be undergoing external stakeholder review by the following groups: Canadian Pharmacists Association, Canadian Nurses Association and the College of Family Physicians of Canada. Moving forward, we plan to engage patient advocates earlier in the guideline development process, but will note that as a limitation for this current guideline.
23. *Secondly,* the interpretation of Study 2 appeared biased towards favoring deprescribing over continuation. The Mean difference in A1C was 1.1% higher in intervention group, but the 95% CI crosses 0. Since a potential harm of deprescribing is the risk of increasing A1C/losing glycemic control, findings cannot rule out that true estimate of effect on A1C could increase by up to 1.6% (UL of CI), which could be a clinically significant depending on pt's baseline A1C... Authors concluded, "Overall, the systematic review suggests that * it is probably not harmful to stop or substitute glyburide (with glipizide), reduce insulin or stop other antihyperglycemics, though neither intervention reduced the risk of hypoglycemia." So both the risk and benefit of Deprescribing is not clear based on results of studies in the SR. i. Perhaps adding a qualifier like "**despite A1C fluctuations, if A1C stable <(%, mean of study participants)** it is probably not harmful to stop or substitute..." to interpretation of results.	Thank you for this suggestion. We agree that an increase in A1C may be clinically significant if baseline A1C is close to target. We have added the following qualifier in to our summary of this trial: "Results of this study suggest that deprescribing antihyperglycemics in elderly nursing home patients whose baseline A1C is well below target does not result in clinically significant A1C increases, and may be safe, though the certainty of evidence was graded as very-low due to its observational design, and concerns over risk of bias, rated as serious, and imprecision." We modified our overall summary to read: "Overall, this systematic review suggests that it is not harmful to stop or substitute glyburide (e.g. with glipizide) in community-dwelling elderly patients. Reducing insulin and/or stopping other antihyperglycemics in nursing home patients with an A1C well below target also appears to be safe. Neither intervention reduced the risk of hypoglycemia. Summary of findings tables are presented in Appendix B."

24. As a clinician one of the most user friendly guidelines, is the Canadian Guidelines for Safe and Effective use of Opioids http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_a_v4_5.pdf). Similarly, these GL could have ~4 clusters of recommendations beginning with how to identify hypoglycemia and screen patients for iatrogenic causes i.e. overtreatment, risk factors for hypoglycemia... Deprescribing recommendations (in Box 3) were easy to find. However, the recommendations presented in the format of two lists (pt criteria and recommended intervention) were slightly confusing. I suggest recommendations to may alternatively be presented as follows, and bolding would also help to highlight: "Older adults, who are otherwise healthy and have substantial life expectancy (ie. >10 years), diabetes goals and targets consistent with younger adults (e.g. A1C < 7%) generally should be considered as benefits outweigh risks." "For elderly adults at risk of hypoglycemia (e.g. due to age, overly intense glycemic control, multiple comorbidities, drug interactions, hypoglycemia history or unawareness, impaired renal function or on sulfonylurea or insulin) we recommend, deprescribing antihyperglycemic(s) that are known to contribute to hypoglycemia (strong recommendation, very low quality evidence)." "For elderly adults at risk of other antihyperglycemic adverse effects we recommend deprescribing antihyperglycemic(s) (good practice recommendation)" "For elderly adults, whom benefit is uncertain due to frailty, dementia or limited life expectancy we recommend individualizing glycemic targets to goals of care and time-to-benefit according to CDA and other guidelines that specifically address frailty, dementia and end-of-life (good practice recommendation) and deprescribing accordingly (strong recommendation, very low quality evidence)" "Frail elderly patients, are at higher risk for hypoglycemia and its consequences, and such risks are generally considered to outweigh the benefits of intensive glycemic control. Treatment preferences and goals should be discussed with patients, and antihyperglycemic treatment should be tailored accordingly." "We suggest clinicians weighing the risks and benefits of a particular medication consider the effect size for the increased risk in the context of how frequently the medication is used and the patient's baseline risk." Finally, I suggest rearranging summary of findings of Antihyperglycemic Deprescribing systematic review to after the recommendations rather than at the beginning of the guidelines, in order to better integrate key evidence/studies into rationale that supports deprescribing.	Thank-you for this thoughtful suggestion. Our guideline development process was designed to generate a GRADE based recommendation (in this case, a recommendation based on eligible deprescribing trials to minimize hypoglycemia). We did articulate two other recommendations, based on 'good practice' regarding minimizing adverse effects (other than hypoglycemia) and individualizing blood glucose targets in frailty. The remainder of the suggestions noted by the reviewer, are not recommendations per se, but rather suggestions as per current guidelines. We have constructed a user-friendly decision-support algorithm which we feel will guide the user. In terms of the order of content, we are working with the journal editors at PLOS ONE to establish a standard format for a collection of deprescribing guidelines.

25. ASIDE: Minor editing needed for... 1. Knowledge Gaps (Page 19) awkward closing sentence: "Lastly, research is necessary to investigate optimal methods of delivering this proposed intervention, and dialogues need to be opened (with) clinicians and policy makers to educate them regarding how and why treatment paradigms are changing in this population, especially given the aging population and regulated environment of long term care settings." 2. Appendix: Table 3 title, should this say "likelihood to cause HYPOglycemia"?	Thank you for identifying this issue. The suggested edit has been included in the guideline. We have corrected the title of Table 3
26. Table 5 and 6, what is rationale for order of medications listed? If none suggest alphabetical.	We have arranged Tables 5 and 6 to be in alphabetical order.
27. lack of information available about how final decisions were made, was there a voting system or informal consensus process? What were areas of disagreement and the methods for resolution? Suggest adding high-level info about the voting process and how it was done via email to the "Evidence to Recommendation" section page 4-5. Below I've paraphrased Cody's description, I think it would be very helpful to users not familiar with the methods paper. But it's still not clear whether the suggestions in clinical considerations also voted on using this process? *The recommendation was sent out by electronic mail to all GDT members to vote either in agreement or disagreement with recommendation. Voters had the choice to respond either privately, direct to GL lead, or to the whole group. In the event of disagreement, the issue was brought forth to the whole team and resolved via discussion. Any changes to the recommendation required a new vote. Our cut-off for consensus was 80%, though all investigators approved of the final recommendation in this case.*	A high-level description of the recommendations voting process had been added to the "evidence to recommendations" section. Clinical considerations represent clinical experience and were not voted upon. The methods for this process are outlined in our Methods publication.
Reviewer 4 (Pharmacist)	
28. Firstly, the guideline is for people aged >65 years as stated in the scope on page 2. The PICO does not refer to age, however, this was adequately addressed in the text immediately following the PICO. We did, however, consider if it was potentially redundant to include age as a risk factor for hypoglycaemia considering the target population is patients aged >65 years. While we can appreciate that there is a range of patients with varying physical, functional and cognitive status over 65 years, we would also like to state that both Beers criteria and STOPP criteria list sulphonylureas as inappropriate for patients aged >65 years, as stated on page 9. Therefore please consider removing "due to age."	We agree that the Beers and STOPP criteria have chosen >65 as their indicator for "elderly" and at risk. By including >65 as the target population, we trust that these recommendations affect the same population. However, there was significant disagreement within the team about whether having someone turn 65 automatically put them at higher risk for hypoglycemia than at age 64. There was agreement, however, that advancing age contributed to higher hypoglycemia risk. We have therefore modified "due to age" to "due to **advancing** age".

29. Secondly, Table 4 provides a thorough list of medications that may interact with antihyperglycemic medications and increase the risk of hypoglycaemia. Please consider expanding the text on page 8 to include some additional medications. For example, while the text includes long-term medications including beta-blockers and monoamine oxidase inhibitors, it could be expanded to include short course medications, such as trimethoprim-sulphamethoxazole as these sometimes get overlooked in clinical practice.	This example has been added to the section about drug interactions.
30. Thirdly. It appears a word is missing after 7000 on page 10 under "Values and patient preferences..." It would read better as "Cross-sectional studies of over 7000 people with type 2 diabetes"	Thank you for pointing this out. We have added your suggestion to page ten to read "Cross-sectional studies of over 7000 **people** with type 2 diabetes…".
31. Fourth. As table 4 is so well constructed, it is a shame not to reference it under the heading "What to do if hyperglycemia occurs" Perhaps add Table 4. after "(e.g. metformin)"	Thank you for this suggestion. Table 4 has been referred to after this statement.
32. I particularly like your paragraph on A1C measurements being potentially misleading in this population. Preventing unnecessary and unwanted pathology is beneficial to the health system as well as patients.	Thank you for this comment.
Reviewer 5 (Family Doctor)	
33. Key points: "We suggest deprescribing of antihyperglycemic drugs to meet individualized targets, particularly if they are experiencing adverse effects or are frail, have dementia or limited life expectancy." (pg. 3) This point could be written more clearly	We have revised this to read: We recommend deprescribing of antihyperglycemic drugs to meet individualized targets, particularly if a patient is experiencing adverse effects or is frail, has dementia or limited life expectancy."
34. "The benefits of glucose control in reducing the risk of diabetes-related complications have been well described." (pg. 3) Would add "in young adults"	The addition of "young adults" may lead to confusion with some readers due to various definitions of the term (e.g. 18-25, 18-50).
35. There's also the work showing hypos in T2DM are associated with increased risk of later dementia - even one major hypo per year. You could make a statement on costs of this care and importance of this outcome to patients....I see you've made this point later but Id think about putting it up front - the costs of care for patients with dementia and the prevalence make this important (pg. 3)	We were not able to find a study demonstrating the hypoglycemia-related dementia risk costs. We do highlight in the resource implications section, the increased health care cost burden associated with those who experience hypoglycemia. However, to extrapolate dementia costs for those who may have been at increased risk due to hypoglycemia is challenging, and perhaps offset by literature suggesting that hyperglycemia increases risk of cognitive impairment. This area represents an important knowledge gap.

36. " Given the inherent risks of hypoglycemia and related morbidity, the difficulty coping with pill burden, and requirements for glucose monitoring for older adults," (pg. 3) I wonder about restating these risks as the 'aim' of the guideline ("to reduce....) to line up more with the AGREE framework which has examples of aims along these lines	This sentence was changed to "We selected antihyperglycemics as an important class for developing a deprescribing guideline to reduce the risks of hypoglycemia and related morbidity, as well as the burden of pill-taking." We removed the phrase "requirements for glucose monitoring for older adults" because our guideline does not specifically address this (other than to reiterate CADTH recommendations regarding frequency of monitoring)
37. **"and** who are a) at risk of hypoglycemia (e.g., due to age, overly intense glycemic control, multiple comorbidities, drug interactions, hypoglycemia history or unawareness, impaired renal function or on sulfonylurea or insulin) or other adverse effects," rather thn restricting to insulin and sulphonylureas, if you say 'on diabetes treatments with known potential for hypoglycaemia' this future proofs for new classes (plus if you look at the licensing trial data, some of newer gents still cause hypos, just lower rate) (pg. 4)	We have left this phrase as is for the time-being as these are provided as examples only and thus do not preclude consideration of other agents. Insulin and sulfonylurea drugs are most widely known for contributing to significant hypoglycemia. We will revisit these examples in the future and will update as needed.
38. "Primary outcomes included: rates of hypoglycemic and hyperglycemic events, change in A1C and proportion of patients experiencing cardiovascular complications. Secondary outcomes included: outcomes associated with hypo or hyperglycemia (e.g., falls, emergency room visits, hospitalizations, seizures), quality of life, patient satisfaction measures, pill burden, and death." (pg. 4) ?microvascular complications of diabetes. These cld all be grouped under 'loss of potential effectiveness'	Thank you for your suggestion. Our outcomes were developed *a priori*. Microvascular complications were considered under outcomes associated with hypo or hyperglycemia. We hesitate to regroup outcomes after our systematic review has been completed, and would like to report them according to how they were developed.
39. These should link directly to the stated reasons / need for this guideline / deprescribing in this group so I wonder if you shd explicitly mention monitoring burden - even though there wont likely be any data it is part of Qol and youve explicitly stated it in your aims / risks / need for a guideline so it provides a link back to this. (pg. 4)	Reduction in monitoring burden has been removed from the aims as the guideline does not specifically address this (other than to reiterate CADTH recommendations regarding frequency of monitoring.
40. "Therefore, in older adults, who are otherwise healthy and have substantial life expectancy (ie. >10 years), diabetes goals and targets consistent with younger adults (e.g. A1C < 7%) generally should be considered" (pg. 7) Although you could also mention / consider here the risk of subsequent microvascular complication development at different levels of HbA1C which drops off markedly where age of diagnosis is 65 or older	We were unable to locate specific references that illustrate that risk of microvascular complications falls with different levels of A1C when the diagnosis is at 65 or older.

41. "Metformin is associated with vitamin B12 deficiency but not lactic acidosis.38,39" My understanding is that this is now controversial in that more sophisticated lab measures to estimate B12 deficiency show metformin lowers the plasma level as measured but does not change cellular level markers of B12 metabolism (ie is not deficiency just plasma measure)	The harms section was conducted as a review of reviews (i.e., compiled information only available through systematic reviews). The intention of the section is to provide an overview of considerations for clinicians and we acknowledge as a limitation that this therefore does not include discussion of potential mechanisms of action or controversy over clinical importance. We have therefore added the following limitation "This approach highlights important hamr considerations but does not explore detailed mechanisms or controversies associated with clinical importance."
42. "In whom benefit is uncertain due to frailty, dementia or limited life expectancy" (pg 13) Is this defined at all in any of the papers. I think once beyond the boundries of 'end of life' this term generated uncertainty in interpretation. It might be good to include life tables with the categories of average life expectancy for fit and frail older adults in different age brackets, along with any helpful or pragmatic definition the team might have formed after the from the systematic review, of limited life expectiancy is significnat in the case of diabetes Rx??	Approaches to estimating life expectancy are not operationalized in any of the guidelines cited. A statement has been added to the paragraph on appropriate targets in those with cognitive impairment, dementia or limited life expectancy "Tools that help estimate life expectancy are available for but do not provide exact time-to-death values, and to our knowledge, have not been used to guide diabetes treatment."
43. "With regards to time to benefit for avoiding diabetic complications 5-10 years of treatment has been shown to reduce risk, or progression of microvascular disease and non-fatal MI" (pg. 14) see prev comment about reduced association over 65 with the same HbA1C levels. Ann Int Med 1997 epidemiological study. I believe theres also some more basci science evidence of a protective effect of glycemia on cell function at older age - similar to the reversal of the cholesterol effect. I could have a look back for the references if youre interested.	We reviewed this reference but did not add a description to the guideline because we could not see how it could contribute to the decision to deprescribe medication, or to the recommendation to individualize targets (the latter based on current guidelines which did not appear to take this reference into account).
44. "The Canadian Diabetes Guidelines have adopted an individualized approach to targeting A1C, Figure 1." (Pg 15) ? note that these are all consensus based as the lead-in sentence.	All guideline development enterprises use consensus to some extent as they synthesize evidence. Acknowledging varying degrees of consensus approaches amongst the different guidelines cited would not change our recommendation or necessarily lend credence to one guideline over another. Therefore, we have elected to not include a statement indicating that other diabetes guidelines are consensus-based.
Reviewer 6 - Endocrinologist	

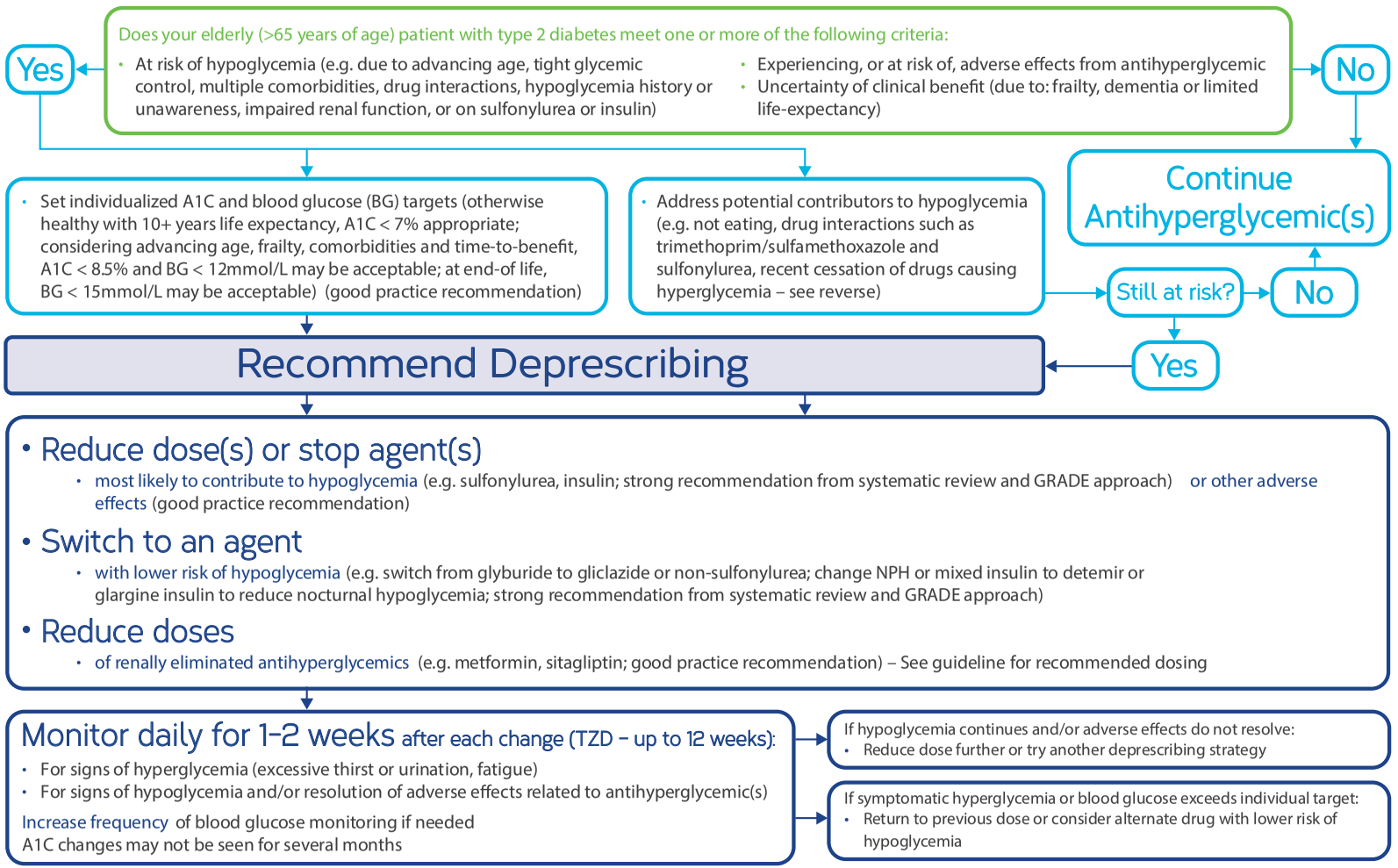
45. this is not a conventional guideline document and so I expected to see something quite different when I started reading it. I think you should re-consider whether this is truly a guideline or a comprehensive review.	We agree this is not a conventional guideline. In order to make decisions about deprescribing, clinicians need to consider the benefit (e.g. evidence for symptomatic, microvascular and macrovascular benefit) and risk (e.g. hypoglycemia and other adverse effects, burden) of continuing a medication and the benefit (e.g. less hypoglycemia and burden) and risk (e.g. worsening symptoms, micro and macrovascular morbidity) of reducing or stopping the medication. We have attempted to provide this information through a combination of narrative review, review of reviews, systematic review and expert opinion on clinical considerations using an accepted methodology for making guideline recommendations (AGREE II, GRADE). All guidelines contain similar varying levels of review. Recommendation strength takes into account the results of the reviews of benefit, harm (of both continuing or reducing medication use) as well as patient preferences and resource implications (such as what was available for review). We acknowledge deficiencies in the review process in the Knowledge gaps section of the guideline.
46. I think there needs to be some indication of the expertise in the GD	A description of each member of the guideline development team has been added in a table.
47. I don't immediately see the links between the text and the Appendices	All of the appendices are identified and cited within the text. APPENDIX A (GDT MEMBERS, expertise and conflicts of interest) APPENDIX B (SUMMARY OF FINDINGS FROM THE SR) APPENDIX C (HARMS SUMMARY) THEN APPENDIX D (THE EVIDENCE TO RECOMMENDATIONS TABLE) THEN APPENDIX E (WHICH WILL BE THE TABLE INDICATING WHICH STAKEHOLDERES HAVE ENDORSED THE GUIDELINE)
48. the document could do with some editing. In places there is a lot of detail and a fair amount of repetition, e.g. recommendations and immediately repeated in Box 3.	We followed a standard guideline template (from CMAJ) to prepare the guideline draft for clinical review. Further editing and formatting will take place in collaboration with target journal editors to find a balance between minimizing replication and highlighting key recommendations for readers.

49. if the point of this paper is deprescribing the emphasis should be on how to deprescribe once the decision is made. As it stands now the paper is a review of all of the current guidelines for diabetes control as developed by learned societies. So it is hard to see what this contribution adds.	We agree that many clinicians often simply want to know HOW to accomplish deprescribing once the decision is made. However, we have also found that clinicians find making the decision to deprescribe challenging. In order to do this, they need to consider the ongoing benefit (e.g. evidence for symptomatic, microvascular and macrovascular benefit) and risk (e.g. hypoglycemia and other adverse effects, burden) of continuing a medication and the benefit (e.g. less hypoglycemia and burden) and risk (e.g. worsening symptoms, micro and macrovascular morbidity) of reducing or stopping the medication. We have attempted to provide this information through a combination of narrative review, review of reviews, systematic review using an accepted methodology for making guideline recommendations (AGREE II, GRADE). Recommendation strength, guided by the GRADE process, also takes into account patient preferences and resource implications. The review of other guidelines is included to help readers understand how this new guideline fits with or differs from the existing published guidelines.
50. Both papers cited as evidence for deprescribing (ref 11 and 12) are cited as weak for evidence and of poor design. And yet they are central to the argument for deprescribing.	Agree. This is why the quality of the recommendation is considered very low. It could change if better quality studies meeting the criteria for inclusion are published. The recommendation itself is based on more than just these 2 studies, including reviews of harms, patient values and preferences and resource use.
51. The argument about absence of benefit of tight glycemic control in older persons is highlighted in Lancet Diabet Endocrinol 2016;4:148-158 and 10.1016/S2213-8587(16)00043-7	This paper presents a very helpful overview of the associations between diabetes and glycemic control, as well as the limitations of the literature. We have made reference to it in the section on Knowledge Gaps.
52. I think the issues in the paper that are directly relevant to hypoglycaemia - and in particular wrt to the target population the frail elderly - should be grouped and presented upfront rather than at the end.	We followed a standard guideline template (from CMAJ) to prepare the guideline draft for clinical review. Further editing and formatting will take place in collaboration with target journal editors to find a balance between minimizing replication, order of presentation and highlighting key recommendations for readers.
53. the deprescribing section can be shortened and many of the points can be dealt with in tables	We followed a standard guideline template (from CMAJ) to prepare the guideline draft for clinical review. Further editing and formatting will take place in collaboration with target journal editors to find a balance between minimizing replication, order of presentation and highlighting key recommendations for readers.

54. what is the point of the tables in Appendix 1 that repeat what is known from other guidelines? And what is the point of tables that identify compounds that produce hyperglycaemia	Table 1 summarizes what is known from other guidelines to help readers decide what targets to individualize for patients. A table is used to minimize main text content. The table that identifies medications known to produce hyperglycemia is included because patients often experience hypoglycemia when a medication that was contributing to hyperglycemia is stopped (e.g. prednisone is stopped but glyburide continued). This is an important first step in assessing or even predicting hypoglycemia, and can help a clinician anticipate that they may need to lower antihyperglycemic doses when stopping another medication known to cause hyperglycemia.
55. I don't understand Appendix C especially the information about antihyperglycemic agents and malignant potential, cardiovascular complications. The information is extraneous to the central issue of hypoglycaemia, unless the time of onset of cardiovascular complications is expected to supervene as a result of hypoglycaemia or add to the burden of disease within the timeframes considered for treatment of frail elderly patients	To make a decision about continuing therapy, or deprescribing, patients and clinicians need also to consider potential harm of continuing therapy (hypoglycemia, plus other adverse effects or associations with disease). A review of review of harms was conducted to provide an overall summary about what is known about the harms of each drug class. We agree that the timeframe of appearance of these associations of adverse effects is important, however the systematic reviews include in our review of review of harms did not provide this level of detail. Only one paper used hazard ratios and these do not speak to the actual time elapsed (only the differences in rates between groups per unit time).

deprescribing.org | Antihyperglycemics Deprescribing Algorithm

March 2016



Farrell B, Black C, Thompson W, McCarthy L, Rojas-Fernandez C, Lochnan H, et al. Deprescribing antihyperglycemic agents in older persons. Evidence-based clinical practice guideline. Can Fam Physician 2017;63:832-43 (Eng), e452-65 (Fr).

deprescribing.org | Bruyère Research Institute | CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

deprescribing.org | Antipsychotic (AP) Deprescribing Algorithm

October 2016

Why is patient taking an antipsychotic?

- Psychosis, aggression, agitation (behavioural and psychological symptoms of dementia - BPSD) treated ≥ 3 months (symptoms controlled, or no response to therapy).
- Primary insomnia treated for any duration or secondary insomnia where underlying comorbidities are managed
- Schizophrenia
- Schizo-affective disorder
- Bipolar disorder
- Acute delirium
- Tourette's syndrome
- Tic disorders
- Autism
- Less than 3 months duration of psychosis in dementia
- Mental retardation
- Developmental delay
- Obsessive-compulsive disorder
- Alcoholism
- Cocaine abuse
- Parkinson's disease psychosis
- Adjunct for treatment of Major Depressive Disorder

Recommend Deprescribing

Strong Recommendation (from Systematic Review and GRADE approach)

Taper and stop AP (slowly in collaboration with patient and/or caregiver; e.g. 25%-50% dose reduction every 1–2 weeks)

Stop AP
Good practice recommendation

Continue AP
or consult psychiatrist if considering deprescribing

Monitor every 1-2 weeks for duration of tapering

Expected benefits:

- May improve alertness, gait, reduce falls, or extrapyramidal symptoms

Adverse drug withdrawal events (closer monitoring for those with more severe baseline symptoms):

- Psychosis, aggression, agitation, delusions, hallucinations

If BPSD relapses:

Consider:

- Non-drug approaches (e.g. music therapy, behavioural management strategies)

Restart AP drug:

- Restart AP at lowest dose possible if resurgence of BPSD with re-trial of deprescribing in 3 months
- At least 2 attempts to stop should be made

Alternate drugs:

- Consider change to risperidone, olanzapine, or aripiprazole

If insomnia relapses:

Consider

- Minimize use of substances that worsen insomnia (e.g. caffeine, alcohol)
- Non-drug behavioural approaches (see reverse)

Alternate drugs

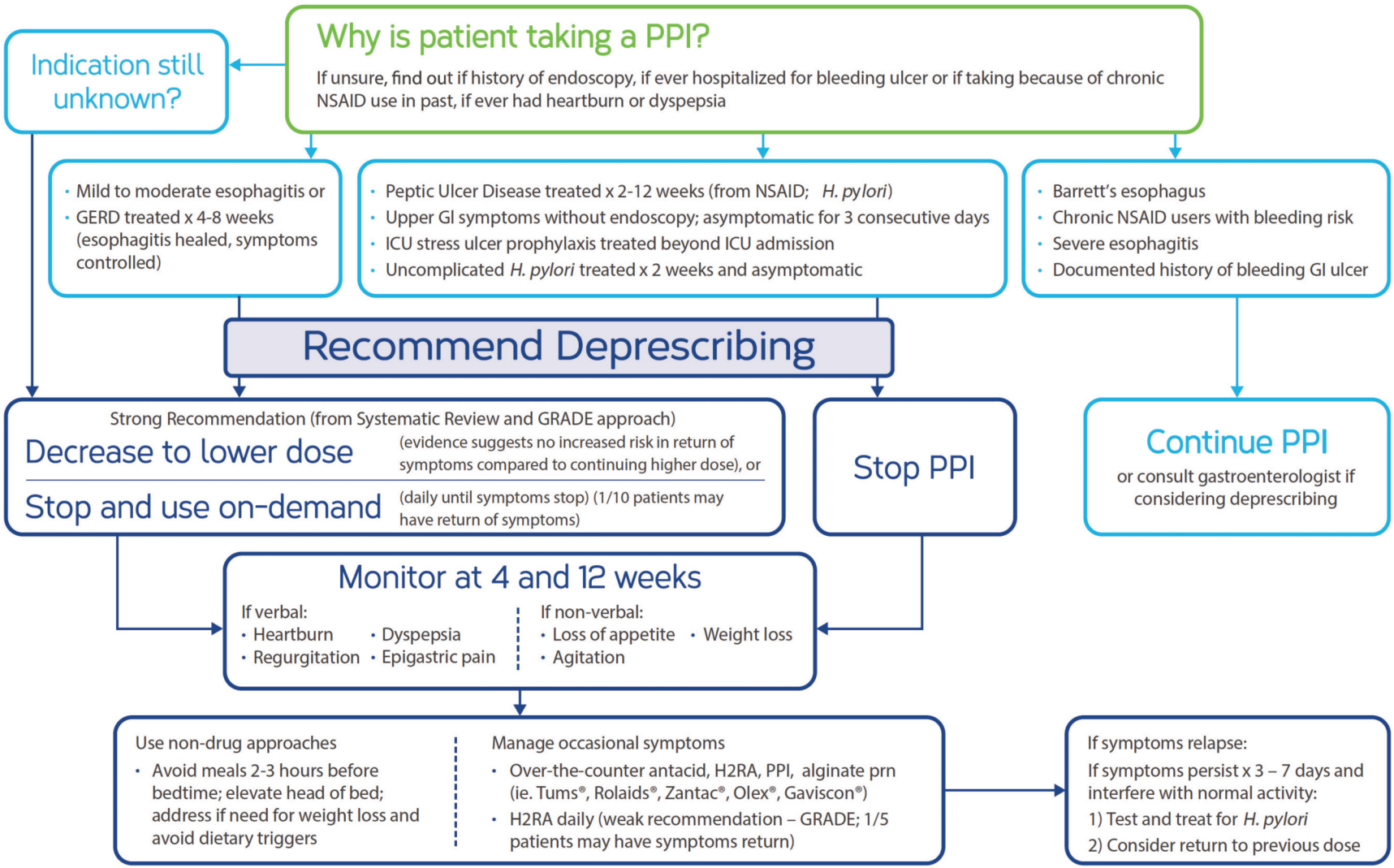
- Other medications have been used to manage insomnia. Assessment of their safety and effectiveness is beyond the scope of this deprescribing algorithm. See AP deprescribing guideline for details.

Bjerre LM, Farrell B, Hogel M, Graham L, Lemay G, McCarthy L, et al. Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia: Evidence-based clinical practice guideline. Can Fam Physician 2018;64:17-27 (Eng), e1-e12 (Fr).

deprescribing.org | Institut de recherche Bruyère Research Institute | OPEN Ontario Pharmacy Research Collaboration

deprescribing.org | Proton Pump Inhibitor (PPI) Deprescribing Algorithm

September 2016



Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ, et al. Deprescribing proton pump inhibitors. Evidence-based clinical practice guideline. *Can Fam Physician* 2017;63:354-64 (Eng), e253-65 (Fr).

deprescribing.org | INSTITUT DE RECHERCHE Bruyère RESEARCH INSTITUTE | open ONTARIO PHARMACY RESEARCH COLLABORATION

deprescribing.org | Benzodiazepine & Z-Drug (BZRA) Deprescribing Algorithm

September 2016

Why is patient taking a BZRA?

If unsure, find out if history of anxiety, past psychiatrist consult, whether may have been started in hospital for sleep, or for grief reaction.

- Insomnia on its own OR insomnia where underlying comorbidities managed
  For those ≥ 65 years of age: taking BZRA regardless of duration (avoid as first line therapy in older people)
  For those 18-64 years of age: taking BZRA > 4 weeks

- Other sleeping disorders (e.g. restless legs)
- Unmanaged anxiety, depression, physical or mental condition that may be causing or aggravating insomnia
- Benzodiazepine effective specifically for anxiety
- Alcohol withdrawal

Engage patients (discuss potential risks, benefits, withdrawal plan, symptoms and duration)

Recommend Deprescribing

Continue BZRA

- Minimize use of drugs that worsen insomnia (e.g. caffeine, alcohol etc.)
- Treat underlying condition
- Consider consulting psychologist or psychiatrist or sleep specialist

Taper and then stop BZRA

(taper slowly in collaboration with patient, for example ~25% every two weeks, and if possible, 12.5% reductions near end and/or planned drug-free days)

- For those ≥ 65 years of age (strong recommendation from systematic review and GRADE approach)
- For those 18-64 years of age (weak recommendation from systematic review and GRADE approach)
- Offer behavioural sleeping advice; consider CBT if available (see reverse)

Monitor every 1-2 weeks for duration of tapering

Expected benefits:

- May improve alertness, cognition, daytime sedation and reduce falls

Withdrawal symptoms:

- Insomnia, anxiety, irritability, sweating, gastrointestinal symptoms (all usually mild and last for days to a few weeks)

Use non-drug approaches to manage insomnia

Use behavioral approaches and/or CBT (see reverse)

If symptoms relapse:

Consider

- Maintaining current BZRA dose for 1-2 weeks, then continue to taper at slow rate

Alternate drugs

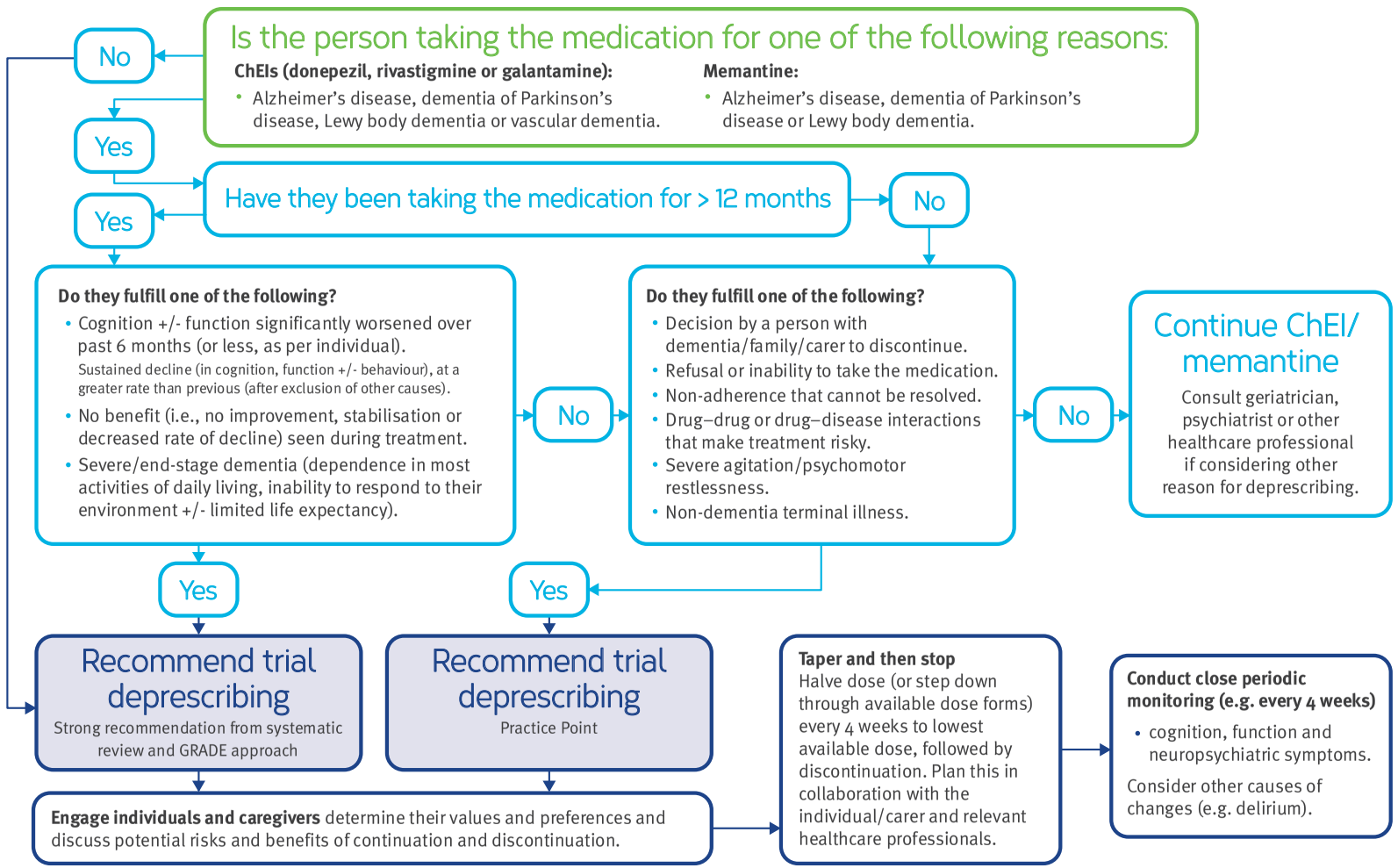
- Other medications have been used to manage insomnia. Assessment of their safety and effectiveness is beyond the scope of this algorithm. See BZRA deprescribing guideline for details.

Pottie K, Thompson W, Davies S, Grenier J, Sadowski C, Welch V, Holbrook A, Boyd C, Swenson JR, Ma A, Farrell B (2016). Evidence-based clinical practice guideline for deprescribing benzodiazepine receptor agonists. Unpublished manuscript.

deprescribing.org | Institut de recherche Bruyère Research Institute | OPEN Ontario Pharmacy Research Collaboration

deprescribing.org | Cholinesterase Inhibitor (ChEI) and Memantine Deprescribing Algorithm

January 2018



Reeve E, Farrell B, Thompson W, at al Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine. 2018.
ISBN-13: 978-0-6482658-0-1 Available from: http://sydney.edu.au/medicine/cdpc/resources/deprescribing-guidelines.php

deprescribing.org | Bruyère Research Institute | Cognitive Decline Partnership Centre | The University of Sydney


deprescribing.org

open
ONTARIO PHARMACY
EVIDENCE NETWORK

Ontario

INSTITUT DE RECHERCHE
Bruyère
RESEARCH INSTITUTE

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

CENTRE FOR AGING
+ BRAIN HEALTH
INNOVATION
Powered by Baycrest