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Abstract

One area of focus of the Bruyère Evidence-Based Deprescribing Guidelines Symposium held in March 2018 was encouraging the routine inclusion of deprescribing recommendations in clinical guidelines. Clinical guidelines often do not accommodate frailty or patients with multiple comorbid conditions. This can give rise to complex medication regimens and risk of medication harm. Despite monitoring and stopping treatment being a key part of rational prescribing, deprescribing is often overlooked in general and in the context of guidelines. There are several challenges to increasing deprescribing recommendations in clinical guidelines. These include limited evidence on the effects of deprescribing, lack of awareness among guideline developers, potential conflicts of interest, and lack of incentives for deprescribing research. To date, medicines regulators, payers, governments, and journals have not encouraged the inclusion of deprescribing recommendations in guidelines. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system could address some of these challenges through its focus on values and preferences, distinct rating of quality of evidence and strength of recommendations, downgrading quality due to indirect evidence, and an explicit approach to conflicts of interest. Further work to adapt GRADE methods to deprescribing could be of benefit. Establishing deprescribing recommendations as a routine part of clinical guidelines is an important opportunity to improve evidence-based clinical practice, and ultimately, patient care.

Keywords: deprescribing, polypharmacy, evidence-based guidelines, GRADE, medication management, research.

Introduction

The 3-day Bruyère Evidence-Based Deprescribing Guideline Symposium was held in Ottawa, Canada, in March 2018. This paper draws on points raised at 2 interprofessional working group sessions on the process and methods of guideline development, and places them in context of the current literature. One group considered the challenges and opportunities in encouraging guideline developers to incorporate deprescribing recommendations within existing guidelines. The other considered developing a deprescribing special interest group of the GRADE system.

Clinical guidelines are defined by the US Institute of Medicine as "statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options".[1] They are intended to provide a source of best evidence that can be integrated with clinical expertise and experience, and patient preference to inform clinician and patient decision-making.[2] Over the past 10 years clinical guidelines have become increasingly influential on health care professionals' practice.[3] Guidelines generally use frequency-based reasoning, using evidence from populations and subpopulations to infer what strategies will "usually" work best for individual patients.[4]

In the early days of guideline development, there were concerns that study populations and health delivery context may not be captured within recommendation statements. Several evidence-based clinical practice groups led by the Cochrane Collaboration have recognized the importance of population and context in rating the certainty of the evidence. For example, when significant variance in population characteristics, context, or interventions exists, the certainty of evidence would be lowered. When developing care plans for real-world patients, clinicians must use best evidence, as well as their clinical experience and contextual knowledge to determine the best approach to patient care.

Single-disease clinical guidelines are typically based on evidence from clinical trials in relatively homogenous patient populations which often exclude older adults or patients living with multimorbidity.[5,6] Suboptimal management may result when these recommendations are applied to more complex patients such as those with multiple comorbidities without clinical judgement, or adaptation to individual needs. Additionally, greater heterogeneity exists in older populations due to factors such as frailty, which is rarely considered in existing guidelines.

People with multiple comorbidities and frail older adults represent a growing proportion of patients yet they are inadequately accommodated in the current framework of clinical guidelines. Applying guideline recommendations to these patients without using equity methods[7,8] or other methods to account for multiple comorbidities[9] can lead to high burden from treatments and their potential harms from dietary and lifestyle recommendations, screening services, and appointments with various health professionals.[10] A systematic analysis of US clinical guidelines illustrates this workload.[11] A person with 3 chronic conditions would be recommended to take 6-13 daily medications, visit a health care provider up to 5.9 times per month, and spend 50-70 hours per month on recommended health-related activities.[11] Guidelines for different conditions may also produce conflicting recommendations and result in dangerous drug interactions.[12] Indiscriminate application of multiple guidelines for a patient with

multiple comorbidities will lead to a complex regimen of multiple medications, and a high risk of drug-drug and drug-disease interactions. However, clinical guidelines seldom provide guidance on managing these burdens.

Prescribing is one of the most common health care interventions recommended in clinical guidelines. As outlined by the WHO Guide to Good Prescribing, rational prescribing should comprise 6 steps (see Figure 1).[13] These steps illustrate that monitoring, including stopping treatment is an integral part of the prescribing process. The WHO suggests that if the patient's problem has been solved, the treatment can be stopped, otherwise, all steps of the rational prescribing process will need to be re-examined, thus highlighting that ongoing assessment of therapeutic objectives and the suitability of treatment(s) is important.

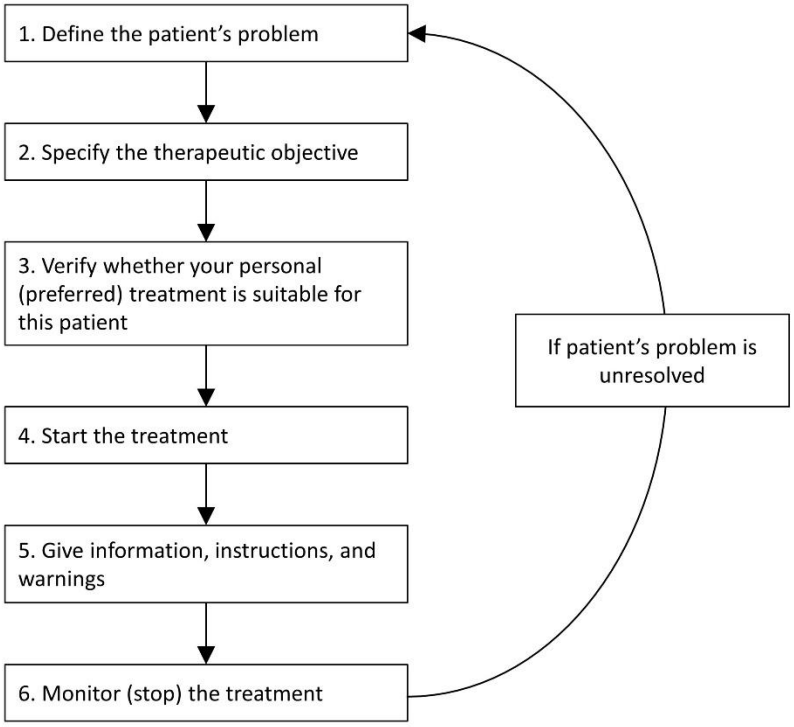

Figure 1: The process of rational prescribing set out in the WHO Guide to Good Prescribing

Following this logic, the process of deprescribing is part of good prescribing practice in the form of ongoing review of appropriateness each time a medication is repeated (i.e., Step 6, followed by an iterative cycle). Yet deprescribing is often overlooked as a key step in general and in the context of clinical guidelines. This may be why the specific term 'deprescribing' is used when discussing this issue. There can be a bias implicit in the language that is used, such that even clinicians who are deprescribing with their patients are still referred to as 'prescribers'. Other issues arise in language used in guidelines where recommendations are either hedged in cautious terms,[14] or are overly definitive using the term 'need' or other commands which may not reflect the quality of evidence, or the strength of recommendations. Clinical guidelines often do not include considerations for stopping or limiting

treatments as part of rational treatment. As such, research groups have created guides for the general process of deprescribing,[15] and specific guidelines for certain medication classes.[16-20] Therefore, just as the WHO guide includes monitoring and stopping treatment, where appropriate, as part of rational prescribing, clinical guidelines should incorporate deprescribing as part of their prescribing recommendations. Deprescribing recommendations can be developed with the same approach and methods used for other recommendations within clinical guidelines (systematic review of benefits/harms etc.),[21] so there may be economies of scale and synergies in routinely considering deprescribing in guideline development. Attendees at the recent symposium discussed a number of reasons why guideline developers may not currently incorporate deprescribing recommendations.

Challenges and opportunities to encourage guideline developers to incorporate deprescribing recommendations

As the body of deprescribing research is limited, evidence regarding benefits and harms of deprescribing, as well as how to deprescribe, may be derived from observational studies, may be of low quality, or may be absent.[22] However, evidence for benefits and harms of prescribing a treatment or optimal treatment duration for older frail patients or people with multimorbidity may be equally lacking.[5,6] In grading their recommendations (e.g. strong or weak), guidelines should consider the quality of the evidence relating to prescribing and deprescribing in such patient populations so that it is explicit where there is limited evidence on continuing a medication, as well as optimal treatment duration. Accordingly, research gaps where additional evidence would be helpful to inform guideline development would become self-evident.

Deprescribing recommendations in guidelines pose different challenges across drug classes. For some medications it may be easy to identify the evidence base to support the net benefits of deprescribing, for example, in the case of benzodiazepines prescribed on a long-term basis to treat insomnia in older people.[16] Conversely, deprescribing benzodiazepines may be difficult due to physical and/or psychological dependence. For other medications such as statins it is more challenging to assess whether stopping treatment is appropriate, as the net benefits and harms of deprescribing are more tightly balanced or less certain, and patient preferences may play a more significant role.[23] In such cases, decision-making may be more difficult for patients and clinicians, but the process of deprescribing may be relatively straightforward.

There is an urgent need to make guideline developers aware of deprescribing initiatives, and of the importance of addressing deprescribing in future clinical guidelines. In its current form, deprescribing is a relatively new concept which is not well-known to guideline development groups. A number of major disease-based guideline developers were invited to the recent deprescribing guidelines symposium, yet only a few were in attendance. It is unclear what strategies would be most effective to influence guideline development groups to consider including deprescribing as an integral part of guidelines. Further research is necessary to improve our understanding of how certain focus areas such as frailty or end of life care come to receive particular attention from clinical guideline development teams. In some cases this may be attributable to one member of the guideline development team raising such an issue.[24] While a number of guideline development handbooks provide some instruction on defining the

scope of the guideline,[25] it is unclear whether guideline developers consider deprescribing recommendations as being within their scope.

Guideline development requires explicit acknowledgement of potential conflicts of interests (COI). Among members of guideline development groups, COIs relating to treatments which may or may not be recommended by the guideline are common. For example, a study of guidelines in the Canadian Medical Association Infobase found that in 75% of guidelines, at least one author disclosed a financial COI with the pharmaceutical industry, over half had at least one author with a COI, and 28.6% had more than half of authors disclosing financial COIs with manufacturers of medications recommended in the guideline.[26] Among European and North American guidelines, an average of 81% of authors per guideline had relationships (potential competing interests) with the pharmaceutical industry, and 59% had relationships with companies whose drugs were considered in the guideline they authored.[27] In relation to deprescribing, it is possible that guideline development team members with conflicts may be more inclined to recommend prescribing of a treatment if they have an interest in it, and they may also be less inclined to recommend deprescribing the treatment.

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Although not a complete impediment to progressing guideline recommendations for deprescribing, it is important to recognise that health care, research, and regulatory environments have not been

conducive to deprescribing, or to the generation of deprescribing evidence. There can be a lack of clinical and financial incentive for deprescribing. Often times, the primary or only incentive may be a clinician's duty to do what is right for the patient.[28] This is balanced, however, against numerous disincentives and barriers such as pay-for-performance models, which can encourage clinicians to overprescribe or ignore the complexity of multiple comorbid conditions.[28-30] Equally, there is little incentive to conduct deprescribing research. Much of the research regarding benefits and harms of medications is carried out by the pharmaceutical industry for product licensing,[31] thus it is not in their interest to generate evidence on when and how to stop treatment. While medicines regulators can mandate further studies be carried out by pharmaceutical companies if evidence at approval is limited (e.g. efficacy based on surrogate endpoints),[32] to date, regulatory bodies have not required evidence related to deprescribing. Existing regulatory mechanisms could potentially be used to produce evidence for deprescribing, thus increasing deprescribing recommendations in guidelines.

Other key stakeholders that could be leveraged to increase deprescribing recommendations within guidelines include payers, governments, and biomedical journal editors. For example, cost coverage of medications could be restricted where there is no evidence for deprescribing recommendations or optimal duration of use. Governments could exert pressure through funding initiatives to address unmet needs. For example, in British Columbia the Physicians Master Agreement has established a Shared Care Committee to improve health outcomes and the patient journey through initiatives on polypharmacy and transitions of care. These types of funding initiatives could support research to inform deprescribing recommendations or groups to advocate for the incorporation of deprescribing recommendations to address issues of polypharmacy. Biomedical journals and professional bodies could exert influence by requiring consideration of deprescribing in clinical guidelines that they publish or endorse.

Using the GRADE approach to address current challenges

The GRADE system has been adopted by over 100 guideline developers as a means of improving rating of quality of evidence and strength of recommendations in clinical guidelines. This approach involves a number of steps (summarised in Box 1), and has several features which may help address some of the challenges of incorporating deprescribing recommendations within existing guidelines.[33]

Firstly, GRADE allows distinct ratings of the quality of evidence as well as the strength of recommendations. This can effectively capture the complexity of cases where systematic review evidence supporting deprescribing may be of low or high quality, but other important factors are considered when formulating the strength of recommendations.[34] GRADE emphasises the importance of patient values and preferences, as well as harms of prescribing/deprescribing and resource use, incorporating them when considering quality of evidence to determine the strength of recommendations.[34]

Furthermore, the system produces separate certainty ratings for each patient important outcome. This can provide an opportunity to explicitly acknowledge the reality of the science through a weak recommendation when evidence is lacking for some outcomes. It also allows a strong recommendation to be made based on weak evidence depending on the clinical context (e.g. to avoid a serious adverse

outcome).[36] The GRADE Working Group outlines how to word recommendations based on both the rating of strength and confidence in the evidence. Stating “we recommend ...” for a strong recommendation suggests that all patients (with the exception of only a small proportion) in the given situation would opt for the recommended course of action. Stating “we suggest…” for a weak recommendation suggests that most patients would opt for the recommendation, but some patients would not. In such cases, clinicians should help patients make decisions consistent with the patients’ values and preferences. For clinicians, a strong recommendation indicates all or most patients should receive the intervention, and a weak recommendation should prompt them to recognize that different choices will be appropriate for individual patients. In the recently published proton pump inhibitor deprescribing guideline there is a strong recommendation for deprescribing based on weak evidence.[20] Although systematic review evidence was of low quality, the recommendation for deprescribing is strong due to lack of serious harm from deprescribing, evidence for benefits in patient important outcomes such as reduced pill burden and reduced risk of side effects, and high societal cost of PPI overuse, as well as the feasibility of a deprescribing intervention.

Box 1: Outline of the GRADE approach for clinical guidelines[35]

Defining the question
- Specifying the population, intervention, comparator(s), and outcomes (PICO)
- Consideration of importance of outcomes (critical, important, or limited importance)

Collecting evidence
- Identify systematic review(s) or plan and prepare systematic review(s)

Rating evidence quality for each outcome (high, moderate, low, very low)
- Initial quality dependent on study design
- Quality of evidence rated down due to risk of bias, inconsistency, indirectness, imprecision, or publication bias.
- Quality of evidence rated up due to large effect, dose response, or if plausible biases mean true treatment effect may be underestimated.

Summarising quality of evidence (evidence profiles) and preparing summary of findings tables

Grading recommendations
- Decide on direction and strength of recommendation (strong or weak)
- Strength dependent on quality of evidence, balance between desirable and undesirable effects, values and preferences, and costs/resource use.

The GRADE approach also requires clearly framing the clinical question using the PICO framework. The result is that the quality of evidence can be downgraded when the population in studies is not representative of the population framed in the PICO (i.e., indirectness in populations).[36] This is particularly important when considering evidence for continuing or for deprescribing medications, given that most clinical trials generally exclude multimorbid, older, and frail patients.[6] Similarly, the outcome

of PICO should specify the time frame of interest,[37] and so when the outcome time frame in studies differs from the typical duration of treatment in real-world use, this indirectness can be explicitly addressed when grading evidence of benefits.

GRADE's transparent and explicit approach means COIs are disclosed, and its defined methodology for grading recommendations reduces their impact.[38] Evidence to support this benefit is available from an evaluation of 2 concurrently developed guidelines (one with COIs and one without COIs which used the GRADE approach) and documented substantial differences in recommendations, particularly in relation to treatments.[39] Using such approaches to managing COIs and limiting the influence of the pharmaceutical industry may lead guideline developers to consider evidence informing deprescribing recommendations on a more equal footing.[40]

The GRADE approach may be one solution that could help to increase deprescribing recommendations within clinical guidelines. GRADE continues to develop as an overarching methodology to guideline development. The standalone evidence-based deprescribing guidelines developed so far have employed GRADE,[21] and further work to adapt the GRADE method to the context of deprescribing could be of benefit. For example, determining how explicit GRADE criteria for assessing the quality of evidence (e.g. dose-response gradient, antagonistic bias) apply in the context of deprescribing, and how undesirable effects are measured and graded.

Conclusions

Historically, clinical guidelines were often based on expert opinion, and attempted to standardise medical care with little flexibility for individual patients' characteristics. Guidelines have progressed to represent sources of best evidence that may be used in conjunction with clinical expertise and experience and patient preference to support optimal treatment decisions.[2] It may now be time to establish consideration of deprescribing within the continuum of treatment recommendations in clinical guidelines as the rule rather than the exception. The routine inclusion of deprescribing recommendations as part of clinical guidelines is a challenging goal, which will take substantial time and effort to achieve. However, this aim is an important opportunity to improve patient care (through reducing use of medications which may no longer be of benefit or may be causing harm) that those who wish to enhance evidence-based clinical practice should endeavour to support.

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Conflicts of interest

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