The future of deprescribing research: seizing opportunities and learning from the past

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There is much to celebrate about deprescribing research. The past decade has seen an explosion of interest in the topic.[1]Recent scholarship has revealed key barriers and facilitators to deprescribing, elucidated effective communication strategies, and developed new measures. Moreover, it has demonstrated the potential for deprescribing to improve outcomes, with meta-analyses finding that intensive deprescribing interventions may reduce mortality and falls in nursing homes by approximately 25%, and that comprehensive medical review may yield similar reductions in mortality among older adults in ambulatory settings.[2,3]

Yet, challenges abound. Many interventions which seemed promising have had disappointing results, and we have gained appreciation of how difficult deprescribing can be. In clinical practice, many people are reluctant to stop medications they were previously told they needed, and clinicians often lack incentive, willingness, or adequate time to make proactive efforts to deprescribe. Even when successful, real-world translation of interventions remains limited, and the push for aggressive medication therapy remains deeply embedded in health systems. Reducing medication count, a common outcome of studies, is not necessarily a win for patients if the discontinued medications were not bothersome or costly to them or their caregivers.

Deprescribing research is thus at a crossroads. While we celebrate initial successes, the easiest work is behind us. As we look ahead, I offer 6 recommendations for how the field can continue to grow, developed from my own reflections, conversations with leaders in the field, and past literature[4] and initially presented as a talk at the first International Conference on Deprescribing in September 2022.

Recommendation #1: Keep doing the "basic science" of deprescribing and use it to inform interventions

Like most scientific endeavors, deprescribing has a translational pathway, beginning with understanding fundamental questions and using the answers to these questions to inform intervention development, testing, and dissemination. Examples of foundational questions include what are the medication problems that merit attention, who has these problems, what stimulates and motivates patients and clinicians to deprescribe in different clinical settings, and what are the right outcomes to measure.

Unfortunately, we have often skipped to designing and testing interventions without fully understanding these upstream questions, resulting in less effective interventions and evaluating the wrong outcomes when we study them. Some aspects of the "basic science" of deprescribing, for example evaluating barriers and facilitators, have been extensively studied. Yet, we have much to learn about many other foundational questions and how to incorporate these learnings into interventions.

Recommendation #2: Lean into behavior change – or bypass it

In many cases, deprescribing is a type of behavior change more akin to promoting smoking cessation than ordering an X-ray or new medication. It requires engaging with patients to stop a medication to which they may have become psychologically or physically attached and enacting that behavior. It also requires convincing overworked and time-pressed clinicians to engage in conversations that may be difficult and time-consuming and to incorporate these actions into their daily clinical practice.

Thus, it is important for interventions to lean into the science and practice of behavior change. A superb example of this is the brochures developed for and tested in the EMPOWER and D-PRESCRIBE trials, which thoughtfully incorporate principles of health psychology and behavior change.[5] Yet, relatively few interventions have followed this lead to incorporate key behavior change elements.[6]

In a notable exception, under the right conditions health system mandates can offer the opportunity to bypass behavior change. This can arise when systems-level changes reduce or obviate the need for action by patients or clinicians. An example of this is policy changes during early phases of the COVID pandemic which temporarily discontinued non-essential medications in nursing home residents.[7]Ethical and legal considerations limit such top-down directives, but in selected circumstances they offer novel opportunities for scholarship and improvement.

Recommendation #3: Be strategic about outcomes

Investigators conducting deprescribing trials often wish to determine the effect of their interventions on "big-ticket" outcomes such as mortality, hospitalization, and quality of life. We can do ourselves a disservice by reaching for these endpoints, as we will often fall short. Given how many factors outside of medication use impact these outcomes, deprescribing interventions may need to have unrealistically potent effects to detect a difference given the limited sample sizes we typically employ. Consider cardiology trials, which often enroll tens of thousands of patients over multiple years to try and achieve such outcomes. And, contrast this with drugs like ezetimibe, which was approved by the US Food and Drug Administration on the basis of beneficial effects on lipid levels without any data on cardiovascular morbidity or mortality.[8] If this is the evidence required to generate widespread use of a drug with well over $1 billion in sales, we may be setting too ambitious a standard for ourselves to attain.

An interesting contrast is set by the OPTIMIZE trial, which used a non-inferiority design and was published in *JAMA* with substantial attention. This study showed that older adults with well-controlled blood pressure (mean systolic, 130 mm Hg) who stopped one antihypertensive medication had similar rates of remaining

at a systolic blood pressure <150 mm Hg than people receiving usual care.[9] This flips the perceived value of deprescribing on its head – rather than having to show that deprescribing improves clinical outcomes, in many settings it may be enough to say that people can fare just as well stopping their medications than continuing them. To be clear, we should not choose outcomes just because they are easy. However, we should pursue opportunities where outcomes are both clinically meaningful and have realistic potential to demonstrate benefit – or, where appropriate, non-inferiority - in response to interventions.

Recommendation #4: Prioritize high-risk groups

In many cases, deprescribing can be beneficial but has only small to moderate effects on outcomes of interest. For example, deprescribing fall-risk increasing drugs (FRIDs) may reduce the risk of falls – yet many other factors influence fall risk, so intervening solely on medications will only go so far. In these settings, testing deprescribing interventions in a population whose baseline risk of the outcome is low almost guarantees that the study will be underpowered to detect small to moderate (but still meaningful) effects.

We should thus test our interventions in populations who have high rates of the outcome we seek to reduce, making it easier to detect a beneficial effect for a given sample size. Consider an intervention that reduces rates of a harmful outcome by one-third (i.e., relative risk 0.67). If the baseline outcome rate among participants in a controlled clinical trial is 10%, a sample size of more than 2300 people would be required to detect the expected reduction from 10% to 6.7% (at P value <0.05 and power of 0.80). In contrast, if 50% of the population has the outcome at baseline, fewer than 300 study subjects would be required to detect the expected reduction in outcome rates.

Recommendation #5: Use out-of-the-box thinking

An adage in quality improvement is that "every system is designed to achieve the result it gets." Why is deprescribing so challenging? Because the health care system is constructed in a manner that foils attempts to deprescribe in manifold ways. Tinkering around the edges of this system is likely to do little good.

Rather, we are likely to have the greatest impact on deprescribing by finding ways to bypass or step outside the system or to co-opt it for our own benevolent ends. For example, changing clinician behavior is notoriously difficult in many health systems. So, some of the most interesting deprescribing interventions have come from bypassing the system and most clinicians, bringing deprescribing messages and behavior change strategies straight to patients.[5] Or, given the difficulty getting busy and overwhelmed clinicians to deprescribe, some pioneers have created their own dedicated deprescribing clinics. There is no single right answer, but in general we are likely to get more traction by embracing innovative, non-traditional approaches that bypass systems-level barriers than by butting up against them.

Recommendation #6: Be a secret agent

Deprescribing is cohering as a professional identity. There are a number of national and regional networks focused on this topic, and the first international conference devoted to the topic was successfully convened in September 2022. While these are positive developments, they come with a danger of becoming insular. We must resist this temptation. Promoting appropriate deprescribing is too large a task for deprescribing-focused researchers and program leaders to take on alone, and the most impactful changes will come by working with partners in a wide variety of research fields and in health systems, guidelines, and governments. Our task is to engage closely with these partners, understand their needs and perspectives, and to bubble up opportunities to promote deprescribing research within those environments aligned with the principles of strategic science.[10] Secret agents covertly infiltrate; we can display our interests more openly but the principles of building relationships, gaining trust, understanding people's interests, and findings ways to align with those interests are analogous.

Conclusions

As we envision the future of deprescribing research, paying careful attention to how our work can be most relevant and impactful will be critical to ensuring that the research we do makes a difference. The six

recommendations discussed in this commentary are hardly comprehensive – for example, they do not address the importance of methodologic rigor – but hopefully will stimulate thinking about how this small but mighty field can successfully grow.

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Box: Recommendations for deprescribing research

1. Keep doing the "basic science" of deprescribing and use it to inform interventions
2. Lean into behavior change – or bypass it
3. Be strategic about outcomes
4. Prioritize high-risk groups
5. Use out-of-the-box thinking
6. Be a secret agent

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