Editorial

Foreword to the first special collection: Addressing the invisible iatrogenic epidemic: the role of deprescribing in polypharmacy and inappropriate medication use

Dee Mangin iD **and Doron Garfinkel** iD

For the International Group for Reducing Inappropriate Medication Use and Polypharmacy

The issues around inappropriate medication use and polypharmacy (IMUP) for individual patients are well known: associations with harmful physical and psychological effects, negative implications for mobility and social interactions as well as the opportunity costs of the sheer burden of treatment. The effect of this problem at the population level is massive. Nearly one-half of older adults take five or more medications, and as many as one in five of these prescriptions is potentially inappropriate.[1,2] Older adults prescribed more medications are more likely to be hospitalized for an adverse drug reaction.[3] Moreover, adverse drug events account for more morbidity and mortality than most chronic diseases,[4,5] with death rates higher than many common cancers.[6,7] The prescribing cascade often attached to inappropriate medication use and polypharmacy drives overdiagnosis and overtreatment, escalating the cost of drugs and hospitalizations.

This threat to health is so significant it has been labelled the first iatrogenic epidemic, yet these data are largely invisible in most standard population measures of quality of care or risks to health.[8] There are screening programs in place in most countries for these other sources of morbidity and mortality: the uncomfortable issue is that, despite the awareness of these problems for some time, there has been little response from the medical system to the harms of polypharmacy. This is likely a reflection of both the complexity of the drivers of the problem and the approach needed to minimize the harmful effects. It also indicates the considerable paradigm shift required to move away from a system predicated on and measured against 'doing'; a system that focuses on translating partial statistical lives of patients with single diseases into the real lives of patients with multimorbidity, with a systematic blindness to how harmful this is. Groups focused on this at national levels are linking globally in the International Group for Reducing Inappropriate Medication Use and Polypharmacy, which provided the impetus for this special collection. This network's goal is to combat IMUP, *via* interdisciplinary communication and collaboration. Representation from 32 countries indicates the pervasive nature of the problem, and enables the strategizing and collaboration and global focus that will likely be needed for the paradigm shift required.[9]

While practitioners are aware of the issue they feel paralyzed by fear and uncertainty in the current framework of care. Moving forward will involve undoing deep-seated ways of thinking about treatment for both clinicians and patients, and reintroducing ideas of variation as a positive attribute, the value of clinical judgement, and of patients as experts. These concepts are not new, but are aligned with the original concept of evidence-based medicine.[10]

What is polypharmacy though? The term polypharmacy is somewhat unclear in conveying the nature of the problem. The most commonly understood functionally important definition of 'many medicines' is five or more medications;[11,12] however, it is hard for patients and often clinicians to conceptualize medicines they understood as 'good' to become 'bad' just because they are

Correspondence to:
Doron Garfinkel
Geriatric-Palliative consultant, Sheba Medical Center and Homecare Hospice, Israel Cancer Association, Israel
dgarfink@netvision.net.il

Dee Mangin
Department of Family Medicine, McMaster University, Hamilton, Ontario, Canada

numerous. The problem is conceptually better articulated and more easily understood as the point when the burden of treatment outweighs the capacity to benefit. A musical metaphor helps. When we listen to a little Bach, or some Leonard Cohen, perhaps Bruce Springsteen or Louis Armstrong played on their own, they make us feel good and our lives better. When played together they become a cacophony that does us more harm than good, and this is what it is like for the patient on multiple medications.

This first special collection of articles maps many of these issues, the route to them and the potential opportunities for reducing their burden and harm. The collection represents the work of some of a global community of clinicians and researchers working collaboratively and with a sense of urgency on finding ways forward. At the highest level the collection illustrates the pervasive nature of the problem. The authors represent groups from around the globe, many also involved in regional and international networks actively focused on reducing, working to understand, and address overmedication. The wide reach of activity around polypharmacy indicates the global system problem in medical care. Pathways of prevention and cure are a useful lens on this epidemic: while treating IMUP by reducing problem medications is necessary, it is not sufficient. Prevention is probably even more important; educating professionals and laymen alike about this critical issue, in an attempt to address the drivers at system level.[9] Several manuscripts in the special collection address the topic of educational programs to doctors, pharmacists, and other health professionals in a variety of healthcare contexts.

This collection foreshadows the way forward; in understanding the supporting frameworks needed, exploration of the effectiveness of explicit drug-based approaches to flagging, for easy recognition, more common potentially inappropriate medicines. These are integrated with approaches highlighting the importance of implicit approaches that take into account patients' experience and priorities. This second part is inseparable from the first; without knowing the patient's priorities or experience it is impossible to provide care that is effective or safe. Similarly, it is essential to include the patient in the conversation as an expert: in their own priorities, in the effects medications have on them, and in the adverse and unintended effects of these medicines.[13] Mangin

et al. show that these conversations are rare, but that until they become routine, shared decision making will not be realized.[13] While rhetoric around care in older adults frequently refers to person-focused or patient-centered care requiring the elicitation of understanding and interpretation in the context of patient priorities, this remains largely rhetoric.

There have been few reports of trials of operationalized frameworks integrating patients' priorities into care. Similarly, there are few approaches to navigating the absence of evidence in the patient with multiple chronic conditions. In their contribution to this special collection, Ouellet *et al.* describe an approach to both that begins with the patient's priorities and then moves to an adaptive practical trial approach that gives high-level direct evidence to inform the trade-off decisions for individual patients.[14]

Developmental evaluation and pragmatic implementation studies may highlight the roadblocks to dispersing these approaches more widely. Using the example of adults with terminal cancer, Juthani-Mehta *et al.* highlight the principles of research design and analyses in vulnerable populations that support the care process, as well as an assessment of the benefits that may well be attenuated compared with the general populations, in trial designs that do not burden patients already burdened by both illness and care.[15]

The single disease approach is one of the ways in which healthcare increases health inequity and addressing polypharmacy carries with it the same risk of increasing health inequity as other interventions to improve care:[16] O'Dwyer *et al.* make the case that particularly vulnerable patient groups (patients with intellectual disability for example) where psychopolypharmacy ensues have no guidance on potentially inappropriate prescribing in these circumstances.[17] Given the underlying disability, the adverse consequences of these medications may have particularly significant effects on function.

Patients today believe that they are taking too many medications and may be open to deprescribing if asked.[18] The need to engage with and empower patients are illustrated in several articles in this collection as well. Empowering patients to begin deprescribing conversations has been shown to be effective.[19] A more detailed analysis

by Turner et al.[20] shows that this, too, is nuanced: the effectiveness of this approach was different for different medication classes, and the internal clinician narrative around deprescribing differed. It was more effective in prompting conversations about proton pump inhibitors (PPIs) than about benzodiazepines, despite the number needed to treat (NNT) for effectiveness for PPIs being more positive.[20] This shows more layers to peel away in understanding the meaning of medicines in peoples' lives, and therefore the significance of not taking them to an individual, including the physiological and psychological effects of tapering.

Evidence for effectiveness of approaches to deprescribing have been disappointing in providing evidence for benefit in terms of health outcomes, however the articles in this collection and others in the literature seem to indicate clear evidence of benefit when champions are carrying out a focused intervention. Embedding these in routine systems of care currently designed to start and continue treatments is challenging. One of the papers by Okeowo et al. highlights just how skewed current systems are towards initiating and multiplying treatments with an inexorable progression of cumulative complexity.[21] They found few if any supports for thinking about the appropriateness of stopping, let alone when and how to do so. Against this background the challenge is likely to be drowned out in the noise of a system that places multiple demands on clinicians and patients who are working in funding frameworks that constrain time. While it is clear than when a service is focused on polypharmacy, change can result. For example, Gnjidic et al., Nachtigall et al., and Petersen et al. describe effective hospital inpatient programs focused on deprescribing prior to discharge.[22–24] Similarly Garfinkel showed positive effects of deprescribing that were sustained longitudinally in a community setting.[25] How to maintain this focus in busy services focused on the multiple needs of complex patients is the challenge. It is not simply the provision of information: the article by Curtin et al. describes the best of the explicit tools that support clinicians in the process,[26] however as the review by Scott et al. describe,[27] it is not a matter of simply integrating these into electronic medical records (EMRs) as decision support. Kouladjian et al. demonstrated, a careful, iterative approach to feasibility that provides a deep understanding of how to integrate these into practice. There is a veritable snowstorm of decision support tools and reminders already in EMRs and, just as form should match function in electronic software, clinical services funding must also match function.

Advocacy is required to emphasize the size of the problem, and its ongoing growth: Chang et al. show that as new drugs emerge and new evidence of adverse effects accumulates, the range of potentially inappropriate medicines increases.[28] Gers et al. show the extent of legacy prescribing in hospitalized patients matches that in community-dwelling patients, and the extent to which drugs are prescribed without an evidence-based clinical indication.[29,30] It is likely that different approaches may suit different geographical and healthcare contexts. What matters is starting. There are needed shifts in attitudes to medication use and medication burden among clinicians and patients. All have been functioning in a system geared to start and continue medications. A system that is focused on single diseases and single drugs, formalized in guidelines also structured along these lines. Turner et al. describe leading strategies to increase public awareness to deprescribing through the general press and media as well as policy initiatives.[31] Inappropriate medication use and polypharmacy with their associated drug adverse effects are now one of the biggest threats to a healthy older age; this represents one of the biggest opportunities we have for improving medical care for older adults.

Conflict of interest statement
The authors declare that there is no conflict of interest.

ORCID iDs
Dee Mangin https://orcid.org/0000-0003-2149-9376

Doron Garfinkel https://orcid.org/0000-0002-3171-9881

References
1. National Center for Health Statistics. *Health, United States, 2016: with chartbook on long-term trends in health*. Hyattsville, MD: National Center for Health Statistics, 2017.
2. Opondo D, Eslami S, Visscher S, *et al.* Inappropriateness of medication prescriptions

to elderly patients in the primary care setting: a systematic review. *PLoS One* 2012; 7: e43617.

3. Canadian Institute for Health Information. *Drug use among seniors in Canada, 2016*. Ottawa, ON: Canadian Institute for Health Information, 2018.

4. Lazarou J, Pomeranz BH and Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; 279: 1200–1205.

5. Lipska KJ, Ross JS, Wang Y, *et al*. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. *JAMA Intern Med* 2014; 174: 1116–1124.

6. European Commission. *Strengthening pharmacovigilance to reduce adverse effects of medicines*. Brussels: European Commission, 2008.

7. Malvezzi M, Bertuccio P, Levi F, *et al*. European cancer mortality predictions for the year 2013. *Ann Oncol* 2013; 24: 792–800.

8. Mangin D, Bahat G, Golomb BA, *et al*. International group for reducing inappropriate medication use & polypharmacy (IGRIMUP): position statement and 10 recommendations for action. *Drugs Aging* 2018; 35: 575–587.

9. Garfinkel D. and Poly-de-prescribing vs. polypharmacy - the weapon to fight an iatrogenic epidemic: an overview. *Eur J Geriatr Gerontol* 2019; 1: 1–10.

10. Sackett DL, Rosenberg WM, Gray JA, *et al*. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312: 71–72.

11. Masnoon N, Shakib S, Kalisch-Ellett L, *et al*. What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017; 17: 230.

12. Gnjidic D, Hilmer SN, Blyth FM, *et al*. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol* 2012; 65: 989–995.

13. Mangin D, Risdon C, Lamarche L, *et al*. 'I think this medicine actually killed my wife': patient and family perspectives on shared decision-making to optimize medications and safety. *Ther Adv Drug Saf*. Epub ahead of print 5 April 2019. DOI: 10.1177/2042098619838796.

14. Ouellet GM, Ouellet JA and Tinetti ME. Principle of rational prescribing and deprescribing in older adults with multiple chronic conditions. *Ther Adv Drug Saf* 2018; 9: 639–652.

15. Juthani-Mehta M and Allore HG. Design and analysis of longitudinal trials of antimicrobial use

at the end of life: to give or not to give? *Ther Adv Drug Saf*. Epub ahead of print 8 February 2019. DOI: 10.1177/2042098618820210.

16. Starfield B, Gervas J and Mangin D. Clinical care and health disparities. *Annu Rev Public Health* 2012; 33: 89–106.

17. O'Dwyer M, McCallion P, McCarron M, *et al*. Medication use and potentially inappropriate prescribing in older adults with intellectual disabilities: a neglected area of research. *Ther Adv Drug Saf* 2018; 9: 535–557.

18. Reeve E, Wiese MD, Hendrix I, *et al*. People's attitudes, beliefs, and experiences regarding polypharmacy and willingness to deprescribe. *J Am Geriatr Soc* 2013; 61: 1508–1514.

19. Tannenbaum C, Martin P, Tamblyn R, *et al*. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the empower cluster randomized trial. *JAMA Intern Med* 2014; 174: 890–898.

20. Turner JP, Richard C, Lussier MT, *et al*. Deprescribing conversations: a closer look at prescriber-patient communication. *Ther Adv Drug Saf* 2018; 9: 687–698.

21. Okeowo D, Patterson A, Boyd C, *et al*. Clinical practice guidelines for older people with multimorbidity and life-limiting illness: what are the implications for deprescribing? *Ther Adv Drug Saf* 2018; 9: 619–630.

22. Gnjidic D, Ong HMM, Leung C, *et al*. The impact of in hospital patient-education intervention on older people's attitudes and intention to have their benzodiazepines deprescribed: a feasibility study. *Ther Adv Drug Saf*. Epub ahead of print 17 January 2019. DOI: 10.1177/2042098618816562.

23. Nachtigall A, Heppner HJ and Thürmann PA. Influence of pharmacist intervention on drug safety of geriatric inpatients: a prospective, controlled trial. *Ther Adv Drug Saf*. Epub ahead of print 16 April 2019. DOI: 10.1177/2042098619843365.

24. Petersen AW, Shah AS, Simmons SF, *et al*. Shed-MEDS: pilot of a patient-centered deprescribing framework reduces medications in hospitalized older adults being transferred to inpatient postacute care. *Ther Adv Drug Saf*. 2018; 9: 523–533.

25. Garfinkel D. Poly-de-prescribing to treat polypharmacy: efficacy and safety. *Ther Adv Drug Saf* 2018; 9: 25–43.

26. Curtin D, Gallagher PF and O'Mahony D. Explicit criteria as clinical tools to minimize inappropriate medication use and

its consequences. *Ther Adv Drug Saf.* Epub ahead of print 13 February 2019. DOI: 10.1177/2042098619829431.

27. Scott IA, Pillans PI, Barras M, *et al.* Using EMR-enabled computerized decision support systems to reduce prescribing of potentially inappropriate medications: a narrative review. *Ther Adv Drug Saf* 2018; 9: 559–573.

28. Chang CB, Lai HY, Hwang SJ, *et al.* The application of updating PIM-Taiwan criteria in clinic-visiting older patients with polypharmacy. *Ther Adv Drug Saf* 2018; 9: 699–709.

29. Gers L, Petrovic M, Perkisas S, *et al.* Antidepressant use in older inpatients: current situation and application of the revised STOPP criteria. *Ther Adv Drug Saf* 2018; 9: 373–384.

30. Mangin D, Lawson J, Cuppage J, *et al.* Legacy drug-prescribing patterns in primary care. *Ann Fam Med* 2018; 16: 515–520.

31. Turner JP, Currie J, Trimble J, *et al.* Strategies to promote public engagement around deprescribing. *Ther Adv Drug Saf* 2018; 9: 653–665.

Visit SAGE journals online
journals.sagepub.com/home/taw

§SAGE journals