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JOURNAL FULL TITLE: Journal of Biomedical Research & Environmental Sciences
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INDEXING & RECOGNITION

- **Indexed in:** Google Scholar, IndexCopernicus (**ICV 2022: 88.03**)
- **DOI:** Registered with CrossRef (**10.37871**) for long-term discoverability
- **Visibility:** Articles accessible worldwide across universities, research institutions, and libraries

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JOURNAL OF BIOMEDICAL RESEARCH & ENVIRONMENTAL SCIENCES
issn: 2766-2276
SUBJECT AREA(S): PUBLIC HEALTH | PHARMACOLOGY | THERAPEUTICS
DOI: 10.37871

LETTER TO EDITOR

Poly-De-Prescribing to Treat the Iatrogenic Epidemic of Polypharmacy - A Major Public Health Challenge

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Introduction

The increase in average lifespan in the last generations is a result of several advances in the medical sciences: improved preventative medicine, the curing of life threatening acute illnesses, and improved management of chronic diseases. Paradoxically, in spite of this success and resulting from it, older adults will experience a time-related increase in the number of incurable co-morbidities. These in turn lead to increased disability and the suffering for prolonged periods of time prior to death [1-3]. There is a rapidly-growing population of vulnerable subpopulations of the very old, those with co-morbidity, dementia, frailty (and disability) and limited life expectancy. We have previously suggested the acronym VOCODFLEX to include all older people who represent one or several of these characteristics [4-7]. The vulnerability of older people increases in correlation to age and to the extent of these characteristics that may obviously overlap and coincide in a single patient. The inability of the workforce to balance the unprecedented medical, economic, and social needs of VOCODFLEX presages a "geriatric boom catastrophe", or burden [8], and "a Tsunami in 21st century Healthcare" [9].

Increased rate and extent of age associated diseases with the rapid increase in vulnerable sub-populations of VOCODFLEX is associated with an increased number of specialists. All these specialists are contributing to the accumulation of drugs leading to Inappropriate Medication Use & Polypharmacy (IMUP).

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DOI: 10.37871/jbres2257

Submitted: 21 November 2025

Accepted: 19 January 2026

Published: 20 January 2026

Keywords

- Poly-De-prescribing; Polypharmacy
- Inappropriate medication use
- Geriatric palliative approach
- Multi morbidity
- Quality of life

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How to cite this article: Garfinkel D. Poly-De-Prescribing to Treat the Iatrogenic Epidemic of Polypharmacy - A Major Public Health Challenge. J Biomed Res Environ Sci. 2026 Jan 20; 7(1): 11. Doi: 10.37871/jbres2257

Causes of IMUP

The increase in the absolute number of older people and COCODFLEX in itself, leads to increased number of medications. Furthermore, each specialist recommends interventions based on the clinical practice guidelines of their field of expertise. Many of these guidelines have no Evidence Based Medicine (EBM) proof for a positive benefit/risk ratio in older people; Boyd, et al. [10] concluded that "adhering to current guidelines in elders with co-morbidities may lead to inappropriate clinical judgment, creates perverse incentives to care, and diminishes the quality of care". Furthermore, the medical system becomes fragmented, with little communication between case manager and specialists especially for the VOCODFLEX. From the specialist's perspective, the paramount concern is preventing morbidity or mortality from "their" disease. Family doctors / General Practitioners (GP) for their part will mostly adopt the specialist's recommendations and rarely interfere or change these treatments. The absence of a single, assertive case manager capable of looking at the big picture, may promote confusion among patients, families, and caregivers. The later may assume a passive role, projecting the burden of authority onto others- a phenomenon known as "the bystander effect" [11]. The result of this diffusion of responsibility is the proliferation of drugs, interactions and Adverse Drug Events (ADE) leading to Inappropriate Medication Use and Polypharmacy (IMUP). Lacking a multi-disciplinary or integrative approach, these trends explain why the epidemic of IMUP is emerging.

Harms of IMUP

IMUP are associated with diverse negative clinical outcomes that include cognitive and functional impairments, delirium, malnutrition and weight loss, falls and hip fractures, incontinence, hospitalizations, nursing home placement, decrease in Quality of Life (QoL) and quality of death, as well as medication non–adherence [12]. Furthermore, IMUP begets IMUP in a vicious cycle of over-diagnosis and over-treatment, with the spiralling cost of drugs and hospitalizations related to ADE placing unbearable financial burdens on healthcare systems [13-23]. In depth discussion of cost related data or published economic analysis is beyond the scope of this manuscript as it concentrates on the medical and clinical aspects of IMUP. However, the number of casualties (Mortality & morbidity) combined with the negative economic and social ramifications justify the definition of IMUP as "The Iatrogenic Epidemic". Nowadays, most health professionals consider IMUP to represent a major hazard to patients and health care systems. Older patients and particularly VOCODFLEX challenge mainstream clinical sensibilities and prescribing patterns; as there are no reliable EBM researches to establish guidelines in older people particularly VOCODFLEX, in an atmosphere of defensive medicine, the medical community globally is extrapolating from the Randomized-Controlled Trials (RCT) performed in robust, much younger and healthier participants applying them to all older people including VOCODFLEX. As the positive benefit/risk ratio of most interventions decreases or becomes negative as older patients join the ranks of VOCODFLEX [10] and near the end of their life expectancy [24], these extrapolations may cause greater harm than good [6,7,10] Nevertheless,, despite the tenuous evidence base, we continue to implement multiple specialty-specific interventions to older patients, irrespective of extreme age and patient characteristics, and often into the palliative stages several years or even weeks prior to death [25,26].

This medical approach is both unprofessional and unethical. No one would dare extrapolate from guidelines proven in adults to include children or babies, so how come we perform

this in another vulnerable subpopulation of older people? We do know that older people are much more vulnerable to adverse drug effects with much higher rate of hospitalizations as the result of adverse drug effects [27]. Nevertheless, even ethical, knowledgeable medical doctors who are aware of the risk of IMUP, continue to prescribe and fill secure believing that they are following the strongest guidelines that rest upon the results of multiple, large RCT. Our older patients (and their doctors) believe we are acting based on RCT based EBM for the benefit of older people as well. In reality, this is not the case. This is a most dangerous situation for patients and doctors: When we as medical doctors know that we don't know for sure - we are much more cautious; when we think we know and believe we act based on the "ultimate truth" of EBM - our hand prescribes with no hesitation.

Given the wide-ranging importance of IMUP for multiple professional fields, an improved understanding of this problem among all care givers and policymakers is essential [4]. Therefore, it is important that all healthcare providers and health authorities should be more exposed to the facts about the epidemic of IMUP and the ways proposed to prevent or reduce it and hopefully, this review represent one step on our way to achieving this goal.

International Efforts and Limitations of Traditional Approaches Suggested to Reduce IMUP

Similar to efforts in other pandemics, a global coalition fighting the scourge of IMUP is crucial and the author has therefore established in 2009 IGRIMUP (International Group for Reducing IMUP), a not-for-profit organization that now contains more than 140 members of different health fields from 26 countries. IGRIMUP's goal is to combat IMUP via interdisciplinary communication and collaboration. IGRIMUP has been involved in several international conferences and collaborative researches and has published a comprehensive position statement including action recommendations for policy, research, and education [5]. There are several other international or continental collaborations that adopt the same goals. However, unlike most epidemics for which specific immunization and treatments are invented quite quickly, despite the countless casualties of IMUP, there is still no general consensus regarding the best method to combat this insidious problem [1-7]. Obviously, for this unique epidemic of IMUP "immunization" should actually involve prevention through better education.

As for tools proposed against IMUP, most geriatricians are familiar with and rely on explicit (Criteria-based) tools such as the Beers criteria [28], the START/STOPP [29] or similar country specific "forbidden drug lists" like FORTA in Germany [30]. They may serve as an alarm system to increase physicians' alertness and avoid specific drugs in elderly patients. However, all these "drugs to avoid" lists and attempts to discriminate "bad drugs" from "good drugs" are basically wrong and misleading. Prescribing 10 to 15 "non-list", apparently "good medications" to older patients is still likely to do more harm than good [31]. It was concluded that drugs-to-avoid criteria are insufficiently accurate to use as stand-alone measures of prescribing quality [32].

An evolution of these strategies are computerized tools such as the PRIMA-eDS [33]. However, similar to "drugs to avoid" lists the use of more sophisticated computerized decision-making support systems resulted in a reduction of the number of medications per patient but with only a modest risk reduction of mortality and hospitalization, with no or only minor improvements in other clinical outcomes or Quality of Life (QoL).

These somewhat disappointing findings may be explained by the fact that all these strategies have missed the bigger picture, perhaps because

they derive from a guidelines-based worldview based on the single-disease model, which posits that patients are largely homogeneous. Such a paradigm is incongruent with the reality of geriatric and multy morbid populations. In these subpopulations heterogeneity is the norm and there is no longer such a thing as natural history of disease, due to the inseparable comingling of multiple diseases with multiple drugs [4,7]. In other words, all these methods concentrate on statistical pharmaco-geriatric findings of the benefit/risk ratio of each drug but do not take into consideration specific patient characteristics.

Advantage of the Palliative Perception and Patient Centered Approaches

A Palliative approach is more appropriate in advanced age and particularly in COCODFLEX; a useful theorem guiding appropriate prescribing for these patients is the Holmes' Pyramid [34] which postulates that as life expectancy decreases, the goals of care focus less on prevention and more on QoL, and the range of appropriate medications contracts substantially. This principle underpins the outsized risk of harm posed by IMUP in older populations

Evidence is accumulating that apart from prevention, the most powerful strategy to combat IMUP is deprescribing [4,6,7,31]. The barriers to deprescribing are great, numbering among them deficiencies in medical education, the practice of defensive medicine, and systematic industry influence [5,12,35,36]. Updated knowledge in geriatrics and pharmacology is important but in order to achieve a patient centered individualization of drug therapy and in line with the palliative perception, we should incorporate patient/family characteristics and preferences.

The Garfinkel Palliative- Geriatric Method (GPGP) and algorithm (Figure 1) have been proposed as a model for poly-deprescribing (PDP); the method is based on the hypothesis that the clinical and economic harm resulting from IMUP outweighs the sum total of all the beneficial effects of the specific drugs de-prescribed. The GPGP involves deprescribing of as many non-life saving medications as possible, emphasizing patient-family autonomy through a high degree of collaboration [3,4,31,36,37]. This algorithm is simple and applicable to all patients, with any combination of comorbidities and medication, and conducive to adoption in a wide range of clinical scenarios. It emulates the original definition of EBM by Sackett DL, et al. [38] 'the integration of best research evidence, clinical expertise and patient values'. The search for reliable best-evidence in older patients and particularly VOCODFLEX may ultimately be fruitless. As such, the GPGP re-emphasizes the prominence originally intended to the latter two, forgotten pillars of EBM - clinical judgment, and giving high priority to patient/family preferences. It is a palliative approach in line with the Holmes framework (34) in which medications with preventive/curative intention of questionable value in their impact on suffering or QoL are stopped. Like the PATH [39] and similar palliative approaches [40,41] that addresses under-prescribing of potentially helpful medications, the GPGP calls for a less aggressive approach in reaching rigid target goals (blood pressure, serum glucose and lipid concentrations).

There is a fair consensus adopting the definition of Gnjidic D, et al. [42] as five drugs representing the cut-off for polypharmacy; beyond this standard, older people experience increased risk of mortality, disability, frailty and falls. In our view, cut-off numbers should not be the main concern, since IMUP can occur with even a single medication. However, there is a consensus that the extent of Inappropriate Medication Use (IMU) correlates to the number of drugs (Polypharmacy) and this fact represents the main pillar for the Garfinkel poly-de-prescribing method. If the main determinant of IMUP is Polypharmacy the solution for the problem should be simply massive de-

prescribing - reducing Polypharmacy as much as possible, an intervention for which we have proposed the term "Poly-de-prescribing" (PDP) [4,6,7].

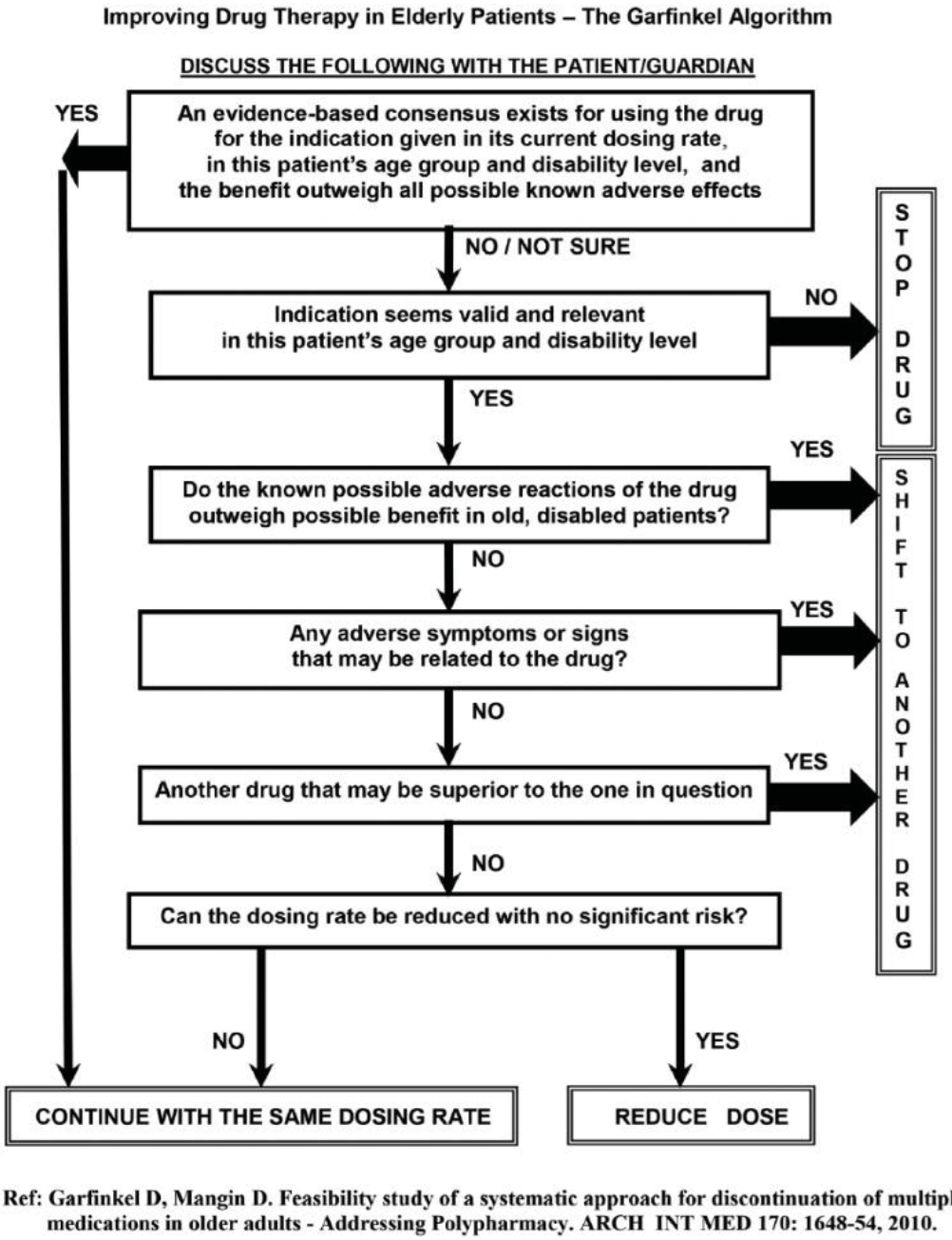
Details of the GPGP method

As we do not wish "to throw out the baby with the bathwater", it should be clarified that Poly-de-prescribing should be distinguished from indiscriminate medication withdrawal; in some patients a drug is changed to a more effective and/or safe medication. Furthermore, if another previously undiagnosed disease is detected, a new medication may be added if indicated. Given the bold nature of this intervention, in the first meeting all recommendations for drug prescription or de-prescription must be explained in depth and approved by the patient/family. The pros and cons of each drug and the risks of IMUP are discussed with the patient and family in an attempt to evaluate the benefit/risk of each drug in the specific patient involved and based on patient/family preferences. Many patients/families propose themselves to stop medications following or even before this discussion. In many cases the decision to deprescribe is made based on the first step of the algorithm (Figure 1) as a positive benefit/risk ratio does not exist for the specific drug for this specific patient's age and characteristics. With patient/family consent, a detailed consultation with recommendations to deprescribe drugs for 3 months only and then rethink, is sent to the family doctor/GP. This approach is practical, professional and most ethical; most people have been repeatedly warned by many health authorities that bad consequences are expected if they do not take all medications until death. Therefore, asking older people to stop drugs for good would be difficult to perceive. As for family doctors, even those who preach for prescribing drugs until death, would agree that stopping medications and particularly preventativive drugs for 3 months only, do not result in increased morbidity or mortality. In the author's experience, after 3 months many patients/families decide by themselves to continue deprescription of most medications, particularly when improvement in QoL is apparent as is usually the case. This also highlights the high role of patient/family autonomy as an important part of the Garfinkel GPGP method. Follow up is an inseparable part of the method and includes updates 3 months after the intervention and then at least once a year.

Evaluating efficacy and safety of the GPGP method

All studies testing the Garfinkel Palliative-Geriatric method and algorithm (GPGP, Figure 1) were performed in older people consuming at least 6 prescription drugs. In two preliminary studies, the GPGP demonstrated efficacy and safety in nursing homes [24] and outpatient settings [31]. The first study was conducted in in 6 nursing departments. Poly-Deprescribing (PDP) was performed in 119 older patients with co-morbidity who were all defined as disabled, most of them were bed ridden and with significant cognitive decline. The control group included 61 comparable older patients in whom no change in medications was performed. They were all treated by the same medical doctors and nurses. After one year out of 331 drugs de-prescribed, only 32 were re-administered (Failure rate of PDP 10%) by the nursing department doctors who were not aware of the study (In order to avoid bias). As compared to the comparable control group who had continued medications "as usual", annual mortality and severe complications requiring referral to acute care facility were significantly reduced in PDP ($p < 0.002$ in both) [24].

The preliminary study in community dwelling older people was published in Arch Intern Med in 2010 [31], De-prescribing was recommended for 311 medications in 64 patients (4.4 ± 2.5 drugs discontinued per patient overall). Of the de-prescribed drugs, 2% were restarted by



Ref: Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults - Addressing Polypharmacy. ARCH INT MED 170: 1648-54, 2010.

Figure 1

the family doctor/GP because of recurrence of original indication, successful discontinuation achieved in 81% with no significant adverse events or deaths attributed to PDP; 88% reported global improvement in health

The method achieved sustained improvements in clinical outcomes in 2 longitudinal studies performed in several hundred older people with follow up of at least 3 years (range 3 - 10 years) [6,7]. Follow up included updates 3 months following the intervention and then, at least once a year. In addition, at the end of the study a detailed, questionnaire assessing QoL, several clinical outcomes and general satisfaction from the PDP intervention was filled by each older patient or, in those suffering from dementia by the primary care giver or guardian. The reaction of the family doctor/GP to the PDP recommendations was also recorded. Length of

follow-up was calculated as time from the first baseline visit until death or until the last follow-up visit and questionnaire, in those who were still alive. The length of follow up was different in different participants but at least 3 years (3-10 years follow-up) in all participants.

Participants were divided into two groups based on the rate of de-prescribing. In the first longitudinal study, the intervention, Poly-De-Prescribers group (PDP) were defined as participants who discontinued ≥ 3 prescription drugs (an average of 6-7 drugs de-prescribed) and the control group those who stopped ≤ 2 medications including those who took the same number or more drugs as compared to baseline meeting [6]. In the second larger and longer longitudinal study, the Poly-De-Prescribers group (PDP) included participants who eventually deprescribed ≥ 50% of their prescription drugs and the control group those who stopped ≤ 50% of the medications taken at the beginning of the study [7]. The main results were similar in both studies: 3 years or more following the poly -deprescribing intervention, as compared to the control group, in participants who performed PDP, there was a statistically significant improvement in functional and cognitive status, sleep quality, appetite, sphincter control, number of serious complications, QoL and general satisfaction from the intervention ($p < 0.002$ in all). The rate of hospitalizations and mortality were comparable. In both studies, refusal of the family doctor/GP to adopt PDP recommendation was the most significant barrier to de-prescribing. The clinical improvement caused by PDP was evident quite quickly, usually within 3 months and persisted for at least 2 years in about two thirds [6,7].

It may be concluded that a rational poly-deprescribing is both effective and safe. Obviously, this approach is associated with huge positive economic consequences.

One may argue that these studies were not RCT and were performed in self-selected older patients who looked for a second opinion being unsatisfied with their health situation, thus not representing the general population of older people. Furthermore, deprescribing and follow up were performed only by a single researcher and represents the experience of one geriatrician (The author). This fact makes it is difficult to distinguish between the benefit of the algorithm and the impact of the author's specific knowledge and experience, which is relevant to others who may wish to replicate this work. Another possible limitation is that the high degree of involvement by the patient and families is time-consuming. However, this element may also reduce medical doctor's fear of lawsuits.

In 2003 Woodward (Woodward) introduced the term "de-prescribing" and defined it as "achieving better health outcomes for older people through reducing medications" [43]. This definition highlights the risk of too many drugs becoming a disease in itself. We take one small step forward proclaiming that the best way to combat polypharmacy is poly- de-prescribing. In other words, not only does IMU increase in correlation to the number of drugs prescribed but conversely, the improvement in IMU negative consequences correlates to the number of drugs de-prescribed, and the intervention is safe and well tolerated. Applying poly-de-prescribing globally may improve the last period of life in millions of older people and also save money – drug cost and cost of hospitalizations resulting from IMUP - a triple clinical – economical win - win situation.

De-prescribing should be regarded as an essential part of good prescribing [44]. However, we've found that refusal of the family doctor/GP to adopt de-prescribing recommendations is still the most significant barrier to de-prescribing [6,7]. Facing the many barriers [12,36,45] and having no guidelines for rational de-prescribing, even knowledgeable and ethical

clinicians lack the confidence to de-prescribe and thus continue to harm their most vulnerable patients, despite the very best of intentions [3,4,6].

Putting it all Together and Moving Forward

Nothing short of a revolution in our clinical thinking will suffice to stem the tide of the devastating IMUP epidemic. Clinicians suffer from the illusion that they do not have a hand in propagating IMUP. In reality, we are all to blame in routinely prescribing too many medications, recommended by too many specialists, to older patients, sometimes until death. Keeping this in mind, other health professional, policy makers and the media should join forces in the attempt to increase the awareness of medical doctors as well as the general public, to consider routine deprescribing for older patients. The proof that rational poly-de-prescribing is safe and associated with beneficial effect on clinical outcomes and QoL that are apparent quite quickly and sustain for several years, should encourage medical doctors to more routinely deprescribe medications as one of the topics addressed in the routine follow up of older people. As stressed in the title of one of the author's publications on the huge extent of polypharmacy in end-of life patients: "Isn't it the family doctor's role to de-prescribe much earlier?" [25].

Despite the many obstacles to de-prescribing [5,12,35,36], there seem to be a positive change in doctors and patient awareness. Attitudes toward IMUP have begun to change, with deprescribing becoming increasingly recognized as a global goal of high priority. Some groups report greater receptiveness on the part of physicians and patients to IMUP and deprescribing especially when educated on the matter in diverse contexts [46-49]. More patients today believe that they are taking too many medications [50,51] and may be open to de-prescribing. Reeve E, et al. [46] conducted a US-population based study and evaluated the attitudes of older adults toward prescribing. The majority of older people were willing to have at least one medicine de-prescribed and did not report distress surrounding this decision. These researches and others conclude that education, of care givers and patients alike, is an essential component in our war to prevent and reduce IMUP; patient attitudes to de-prescribing may be influenced by information acquired through the media stressing that de-prescribing is an essential part of good prescribing [44] We believe that education about de-prescribing must begin earlier as part of the core curriculum in medical, nursing and pharmacy schools. The idea that drugs may eventually need to be stopped, should be instilled early in the general public awareness [48]. Combined, these strategies will hopefully have a large impact on the attitudes of both clinicians and patients. McCahon D, et al. [52] concluded that improved prior communication and information around the intended purpose and potential benefits of medication review may enhance patient engagement and improve patient experience and outcomes. Face-to-face consultation and relationship continuity were considered important for efficient and effective medication review. Above all, as in other topics adopting the palliative perception and as proven in the GPGP method, partnership with the patient and family in decision-making is essential, and a key to overcoming barriers to de-prescribing.

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