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American College of Rheumatology
Empowering Rheumatology Professionals

REVIEW ARTICLE

Optimizing Medication Use in Older Adults With Rheumatic Musculoskeletal Diseases: Deprescribing as an Approach When Less May Be More

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The world population is aging, and the rheumatology workforce must be prepared to care for medically complex older adults. We can learn from our colleagues and experts in geriatrics about how to best manage multimorbidity, polypharmacy, geriatric syndromes, and shifting priorities of older adults in the context of delivering care for rheumatic and musculoskeletal diseases (RMDs). Polypharmacy, a common occurrence in an aging population with multimorbidity, affects half of older adults with RMDs and is associated with increased risk of morbidity and mortality. In addition, potentially inappropriate medications that should be avoided under most circumstances is common in the RMD population. In recent years, deprescribing, known as the process of tapering, stopping, discontinuing, or withdrawing drugs, has been introduced as an approach to improve appropriate medication use among older adults and the outcomes that are important to them. As the rheumatology patient population ages globally, it is imperative to understand the burden of polypharmacy and the potential of deprescribing to improve medication use in older adults with RMDs. We encourage the rheumatology community to implement geriatric principles, when possible, as we move toward becoming an age-friendly health care specialty.

INTRODUCTION

Rheumatologists are highly trained in the use of complex medications to improve care of individuals with rheumatic musculoskeletal diseases (RMDs). Medications such as disease modifying antirheumatic drugs (DMARDs), and their early aggressive use in a treat-to-target (T2T) approach, transformed the landscape and trajectory of rheumatologic care and outcomes (1,2). However, it is critical to examine our approach to managing older adults with RMDs who are prone to the negative effects of medications including increased risk of adverse effects, drug–drug interactions, and drug–disease interactions (3–6). This is all the more imperative and timely as the number of older adults living with RMDs is growing as the world population is aging (7).

Coexisting and competing complexities, such as polypharmacy, multimorbidity (defined as having two or more concurrent comorbidities), and shifting goals/priorities of care, contribute to the unique challenges related to prescribing for older adults. Polypharmacy, a common occurrence in an aging population along with multimorbidity, affects half of older adults with RMDs and is associated with an increased risk of morbidity and mortality (8). Although usually referred to as the concurrent use of five or more medications, there is wide heterogeneity in the definition of polypharmacy ranging from numerical counts only, numerical counts for a given duration of therapy or setting, or descriptive terms such as minor or major polypharmacy (9). Despite variability in the definition, the implied message is that polypharmacy exists when more drugs are being prescribed or taken than are clinically appropriate for the number of comorbidities of a given patient. As Dr. Steinman (10), a national leader in identifying and improving the quality of medication prescribing in older adults, points out, "Numbers aren't the enemy; unnecessary, ineffective and harmful prescribing is."

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Further complicating treatment approach in clinical practice, older adults are often excluded from clinical trials for many of the reasons noted earlier, and we lack age-specific clinical practice guidelines for RMDs. From a cost perspective, DMARDs account for more than half of all direct medical costs related to rheumatoid arthritis (RA), leading to substantial out-of-pocket expenses for individuals (11–13). Moreover, Medicare spending on DMARDs, in particular biologic DMARDs, exceeded $10 billion in 2017 (11,14–16). Therefore, rheumatologists must be prepared to optimize safe and effective medication use in a manner that aligns clinical outcomes and cost considerations in these vulnerable and complex older adults.

In this review, we present fundamental principles of, challenges related to, and need for a continuum of safe prescribing practices in older adults, as applied to rheumatology. We focus on how our field can learn from our colleagues and experts in geriatrics about how we can manage polypharmacy and consider deprescribing as an approach to optimize medication use in the context of delivering patient-centered and goal-concordant care for older adults with RMDs (17).

Tenets of medication use in older adults. Medication prescribing in older adults is associated with unique challenges for several reasons, and rheumatologists need to be vigilant in their therapeutic approach to ensure delivery of high-quality care for older adults with RMDs. First, assessment of medication benefit–harm ratios should be ongoing and frequent in older adults because of the high prevalence of multimorbidity and consequent polypharmacy. Second, akin to other specialties, older adults with RMDs have been traditionally under-represented in randomized controlled clinical trials (RCTs), which reduces the generalizability of pivotal studies to this population. In a systematic literature review, it was shown that the average age of patients with RA included in RCTs was 5.2 years lower than the average of participants in population-based studies (average age of 53.0 vs. 58.2 years) and was 4.7 years lower for those with osteoarthritis (average age of 62.8 vs. 67.6 years) (18). These data underscore the urgent need for efforts to increase the inclusion of older adults with RMDs in clinical studies. Third, there are significant alterations in the pharmacokinetics and pharmacodynamics of numerous drugs in older age (19) that warrant caution when translating evidence from studies conducted in younger participants to the care of older adults with RMDs. Older adults may not experience the same degree of response to treatment and at times exhibit novel or atypical presentation of drug-related adverse events (20–22). Last but not least, an important issue to keep in mind is that with aging, there may be a shift in the goals of care and treatment. Whereas disease-focused outcomes are most commonly evaluated in RCTs, a more comprehensive assessment of goals, patient-reported outcomes, and preferences that include physical, psychological, cognitive, and functional domains are important to consider with medications that are used in routine practice for older adults. These tenets to prescribing align with the geriatric principles of the 4Ms, a set of four evidence-based elements of high-quality care in older adults, consisting of what Matters most, Medication, Mentation, and Mobility (23). Multicomplexity was later added to create the consolidated framework known as the Geriatric 5Ms that helps ensure older adults receive the best care possible, are not harmed by health care, and are satisfied with the care they receive (24).

Polypharmacy among older adults with RMDs. A few studies have attempted to evaluate the prevalence of polypharmacy among individuals with RMDs (8,25). In a single center cohort of older adults with systemic lupus erythematosus (SLE), Seguin et al found a high prevalence of polypharmacy in which almost two thirds were prescribed 5 or more medications and more than one third were prescribed 10 or more medications (25). Compared to older adults without SLE, the percentage on 5 or more prescription medications was more than double among those with SLE and 65 years of age or older (30% vs. 74%) and was almost nine times as high for those taking 10 or more medications (4% vs. 34%). In a large national RA cohort study, Bechman et al (8) found that half of those 65 years of age or older were prescribed 5 or more medications and that polypharmacy was associated with serious adverse events, including death and hospitalization. The high prevalence of polypharmacy is likely related to increased accrual of comorbid conditions in those aging with RMDs and greater burden of multimorbidity at time of diagnosis among those with late-onset RMDs (26,27). Bechman et al found that the likelihood to achieve a clinically meaningful RMD improvement decreased and the risk of serious adverse events increased with each additional medication an individual was receiving in addition to their RMD medication (8).

In addition to multimorbidity, another less recognized contributor to polypharmacy is a phenomenon known as a prescribing cascade, a term described in 1995 by Rochon and Gurwitz (28). A prescribing cascade occurs when a new medication is prescribed to treat adverse side effects of previously prescribed medications that are misdiagnosed as new clinical conditions and, subsequently, lead to inappropriate, unnecessary, or potentially hazardous additional drug use (29). Examples include hypertension due to use of nonsteroidal anti-inflammatory drugs (NSAIDs) leading to antihypertensive use and hyperuricemia resulting for thiazide diuretics leading to gout treatment. Another common prescribing cascade in RMDs relates to the use of high-dose and/or long-term glucocorticoids (GCs), which can lead to additional use of proton-pump inhibitors, antibiotics, and bisphosphonates to manage their adverse effects.

Efforts to accurately ascertain drug-related adverse effects, awareness of prescribing cascades, and interruption of potentially inappropriate and/or suboptimal medications is key to optimizing safe and effective prescribing practices in older adults.

Potentially inappropriate medication use among older adults with RMDs. Concerns about polypharmacy and the subsequent need for effective medication review led to the development of explicit criteria as one way to identify inappropriate medication use in older adults that can guide consideration of benefit-harm for deprescribing. For example, the American Geriatrics Society Beers Criteria provide guidance regarding potentially inappropriate medications (PIMs) that should be avoided under most circumstances or depending on certain drug–disease and drug–drug interactions (30). Older adults with RMDs, including RA and SLE, are at an increased risk of exposure to PIMs such as opioids, antidepressants, and benzodiazepines because of the prevalence of comorbid pain, anxiety, and depression in this population (31–38). The prevalence of depression, for example, among individuals with RA and SLE is estimated to be up to 40% (31,32). Any opioid use is observed in 35% to 60% of adults with RA and SLE (34,36–39). Opioids are commonly prescribed long-term although scientific evidence does not support its efficacy for noncancer chronic pain control, and their use has been associated with a delay in DMARD initiation (34,36,38,40–42). Table 1 summarizes common questions related to use of PIMs in older adults with RMDs.

Deprescribing: the concept, definition, and process for improving medication use in older adults. In the recent decade, deprescribing has been introduced as an approach to reduce the negative impact of PIM use and polypharmacy in the aging population (43–45). Deprescribing is defined as the "thoughtful and systematic process of identifying problematic medications and either reducing the dose or stopping these medications under the supervision of health care professionals, in a manner that is safe, effective, and helps older adults maximize their wellness and goals of care" (46–48). Emerging evidence from RCTs and observational studies show deprescribing improves health related quality of life and, moreover, older adults are willing to consider stopping medication(s) and sometimes even seek this out (49–51).

The key aspect of deprescribing is that this is a complex process that takes into consideration patient treatment goals and involves behavioral change for prescribers and patients. Deprescribing is not simply the opposite of prescribing nor synonymous to withholding effective treatment (52). Medication prescribing is usually informed by disease-specific clinical practice guidelines with strict exclusion criteria that derive data from middle-aged adults and advocate for use of multiple medications but fail to adequately account for complexities related to multimorbidity and polypharmacy that are prevalent in older adults. In the aging population, it is crucial to provide ongoing and frequent assessments of treatment responses and harms and dynamically adjust medications to improve outcomes that are important to them. Deprescribing is part of and aligns with this approach to good prescribing practice and care continuum.

In 2019, with increasing recognition of the role of deprescribing in improving care of older adults in general practice, the National Institute on Aging funded the US Deprescribing Research Network (USDeN) to provide resources and catalyze the development and dissemination of evidence about deprescribing for older adults (53). Moreover, international attention on deprescribing is mirrored in the versatility of USDeN's partners in Canada, Australia, and the United Kingdom and the inaugural 2022 International Conference on Deprescribing hosted in Denmark (53,54). There is also growing interest in deprescribing from medical specialties such as cardiology (eg, statins, antihypertensive, and heart failure medications) and gastroenterology (eg, tumor necrosis factor [TNF] inhibitors [TNFis] for inflammatory bowel disease) (55–58) in their efforts to adopt the Geriatric 5Ms for delivery of age-friendly health care.

The process of deprescribing involves inherent uncertainties involving the identification of medication to reduce or stop and monitoring for adverse drug withdrawal events. Based on review of existing prescribing tools and literature, researchers developed the following five principles of deprescribing protocols (see Table 1): 1) review all current medications and their indications, 2) consider overall risk of drug-induced harm in individual patients to determine the required intensity of deprescribing intervention, 3) assess each drug in regard to its current or future benefit potential compared with current or future harm or burden potential, 4) prioritize drugs for discontinuation that have the lowest benefit–harm ratio and lowest likelihood of adverse withdrawal reactions or disease rebound syndromes, and 5) implement a discontinuation regimen and monitor closely for improvement in outcomes or onset of adverse effects (48,59).

In the following sections, we describe current evidence and available tools to suggest approaches to identifying opportunities for deprescribing PIMs and rheumatic medications for older adults with RMDs (Figure 1).

Deprescribing PIM: evidence-based tools and their effectiveness. Benzodiazepines are PIMs with a clear link to increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults (60). In addition, drug–drug interactions between benzodiazepines and opioids increase risk of overdose. Thus, benzodiazepines have been a target drug of interest among deprescribing researchers. In the D-PRESCRIBE (Developing Pharmacist-Led Research to Educate and Sensitize Community Residents to the Inappropriate Prescription Burden in the Elderly) trial (NCT02053194) (61), 489 community-dwelling adults 65 years of age and older were randomized at the pharmacy level to usual care versus patient-facing education in parallel with provision of physicians with evidence-based deprescribing recommendations. Discontinuation of benzodiazepine rate was higher in the intervention group compared to usual care (43% vs. 9%). Fueled by growing evidence of the efficacy of deprescribing to reduce inappropriate

Table 1. Summary of key considerations, guidelines, and resources for deprescribing prescription medications

Common questions	Comments/approaches
What is deprescribing?	Deprescribing refers to the thoughtful and systematic process of identifying problematic medications and either tapering, stopping, discontinuing, or withdrawing these medications in a manner that is safe, effective, and helps older adults maximize their wellness and goals of care.
How does deprescribing align with geriatric principles?	The underlying reason for deprescribing is polypharmacy. The Institute for Healthcare Improvement promotes adopting the "4Ms," which is a set of 4 evidence-based elements of high-quality care in older adults (what matters, medication, mentation, and mobility) to become an age-friendly health care system. Deprescribing aligns with the 4Ms and is an approach that aims to optimize medication use with consideration for what matters to the older adult and their family caregivers. http://www.ihi.org/Engage/Initiatives/Age-Friendly-Health-Systems
What are the 5 principles of deprescribing protocols?	1. Review all current medications and their indications 2. Consider overall risk of drug-induced harm in individual patients to determine the required intensity of deprescribing intervention 3. Assess each drug in regard to its current or future benefit potential compared with current or future harm or burden potential 4. Prioritize drugs for discontinuation that have the lowest benefit–harm ratio and lowest likelihood of adverse withdrawal reactions or disease rebound syndromes 5. Implement a discontinuation regimen and monitor closely for improvement in outcomes or onset of adverse effects
How to assess potentially inappropriate prescribing in older adults?	The American Geriatrics Society Beers Criteria provides guidance on PIMs that should be avoided by older adults in most circumstances or under specific situations, such as in certain diseases or conditions. The criteria are updated on a 3-year cycle; the most current version is from 2019 and release of updated guidance is anticipated in late 2022. https://agsjournals.onlinelibrary.wiley.com/doi/10.1111/jgs.15767
What is the rationale and recommendation regarding PIMs commonly used by patients with RMDs according to the Beers Criteria?	Antidepressants, alone or in combination: Tricyclic antidepressants and paroxetine are highly anticholinergic and sedating and cause orthostatic hypotension. Selective serotonin reupdate inhibitors may exacerbate or cause syndrome of inappropriate antidiuretic hormone secretion or hyponatremia. Serotonin-norepinephrine reupdate inhibitor are considered PIMs in older adults with history of falls or fractures. Drug–drug interactions of certain antidepressants with other CNS-active medications increase risk of falls and fractures. Duloxetine should be avoided in older adults with CrCl < 30 because of increased GI adverse effects (nausea, diarrhea) Benzodiazepines: Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents. Shorter-acting benzodiazepines are not safer than long-acting ones. In general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults. Drug–drug interactions between benzodiazepines and opioids increase risk of overdose Corticosteroids (if used with NSAIDs): Interaction with NSAIDs, high risk for GI bleeding or peptic ulcer Gabapentin and pregabalin: Dose should be reduced in older adults with CrCl < 60 because of CNS adverse effects. Drug–drug interaction between pregabalin and opioids increase risk of overdose Nifedipine, immediate release: Potential for hypotension, risk of precipitating myocardial ischemia NSAIDs; non-cyclooxygenase-selective: Increased risk of GI bleeding or peptic ulcer disease in high-risk groups, including those >75 years or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents. Risks are dose related. Use of PPIs reduces but does not eliminate risk. Avoid chronic use, unless other alternatives are not effective, and patient can take gastroprotective agent (PPI). May increase risk of acute kidney injury and further decline of renal function in older adults with chronic kidney disease stage 4 or higher (CrCl < 30) **For osteoarthritis pain, topical NSAIDs can be used safely given limited systematic absorption [90]. Indomethacin: Increased risk of GI bleeding/peptic disease and acute kidney injury in older adults. Indomethacin is more likely than other NSAIDs to have adverse CNS effects. Of all the NSAIDs, indomethacin has the most adverse effects Opioids (if used with benzodiazepines, gabapentin, pregabalin): Drug–drug interaction with benzodiazepines, gabapentin, and pregabalin, increasing risk of overdose and risk of severe sedation-related adverse events, including respiratory depression and death. Should be avoided except for pain management in the setting of severe acute pain (eg, recent fracture or joint replacement). Dose of immediate release tramadol should be reduced in older adults with CrCl < 30 because of CNS adverse effects (risk of SIADNH/hyponatremia) PPI: Risk of *Clostridium difficile* infection and bone loss and fractures. Avoid scheduled use for >8 weeks unless for high-risk patients (eg, oral corticosteroids or chronic NSAID use), erosive esophagitis, or demonstrated need for maintenance treatment Skeletal muscle relaxants: Most muscle relaxants are poorly tolerated by older adults because some have anticholinergic adverse effects, sedation, increased risk of fractures
Are there evidence-based guidelines and algorithms for deprescribing in older adults?	Yes, the USDeN has global partners in Canada, Australia, UK, and Europe whose researchers have developed evidence-based guidelines and algorithms for deprescribing: PPIs, antihyperglycemics, antipsychotics, benzodiazepines, cholinesterase inhibitors, and analgesics. These approaches/tools, however, are not rheumatology specific, and development of evidence-based guidelines that incorporate disease activity measures and patient preferences would benefit patients with RMDs. https://deprescribingresearch.org/resources-2/resources-for-clinicians/

(Continued)

Table 1. (*Cont'd*)

Common questions	Comments/approaches
Who are the stakeholders to engage when considering deprescribing?	Stakeholder at the point-of-care may include patients, family members/caregivers, pharmacists, and clinicians. In deprescribing research, stakeholder engagement may be expanded to include community members/partners, payers, industry, hospitals, and other health systems, as well as policy makers to ensure knowledge, insights and perspectives are equitably represented and enhance the relevance and application of research. https://deprescribingresearch.org/; USDeN Stakeholder FAQ:
What are some examples of provider-driven approaches for deprescribing PIMs and other prescription medications?	D-PRESCRIBE (Developing Pharmacist-led Research to Educate and Sensitize Community Residents to Inappropriate prescription Burden in Elderly): Evidence-based pharmacist assisted education and communication targeting both patients and providers regarding inappropriate prescriptions. https://deprescribing.org/news/d-prescribe-trial-harnessing-the-power-of-the-physician-pharmacist-and-patient-triad/ EMPOWER (Eliminating Medications through Patient Ownership of End Results): Direct patient empowerment intervention through education of the risks of benzodiazepine use and a stepwise tapering protocol. https://deprescribing.org/news/empower-trial-empowering-older-adults-to-reduce-benzodiazepine-use/ http://www.criugm.qc.ca/fichier/pdf/BENZOeng.pdf IMPROVE (Initiative to Minimize Pharmaceutical Risk in Older Veterans): Interprofessional, experiential educational program for post-graduate primary care trainees to develop their knowledge and skills in addressing polypharmacy in older adults. Consists of group clinic followed by one-to-one patient–provider shared decision making. https://improvepolypharmacy.yale.edu/ Palliative and Therapeutic Harmonization: Canadian-based resources for deprescribing in frail older adults and palliative care https://pathclinic.ca/ Primary Health Tasmania: Organization under the Australian Government's Primary Health Networks Program that provide guides on deprescribing several medication classes, including allopurinol https://www.primaryhealthtas.com.au/resources/deprescribing-resources/ TRIM (Tool to Reduce Inappropriate Medications): A web tool linking the electronic health record to a clinical decision support system, on medication communication and prescribing. VIONE (Vital, Important, Optional, Not indicated, Every medication has indication): Supports systematic, individualized assessment and adjustment of medication management to reduce polypharmacy risk and improve patient safety, comfort, and medication adherence through 5 filters.
What are some examples of resources related to deprescribing available for patients?	Deprescribing information pamphlets that align with evidence-based deprescribing guidelines and algorithms on medications such as PPIs, benzodiazepines are available online at https://deprescribingresearch.org/for-patients/ Patients can search for information about prescriptions drugs and over-the-counter medicines, including side effects and specials precautions online through the NIH National Library of Medicine at https://medlineplus.gov/druginformation.html
How can older adults access expert medication review?	Medicare plans with drug coverage offer free MTM services if beneficiaries meet certain requirements. MTM includes five core elements: medication therapy review, a personal medication record, a medication-related action plan, intervention or referral, and documentation and follow-up.

Abbreviations: CNS, Central Nervous System; CrCl, creatine clearance; GI, gastrointestinal; MTM, Medication Therapy Management; NSAID, nonsteroidal anti-inflammatory drug; PIM, potentially inappropriate medication; PPI, proton-pump inhibitor; RMD, rheumatic musculoskeletal disease; SIADNH, Syndrome of inappropraite antidiuretic hromone secretion; USDeN, US Deprescribing Research Network.

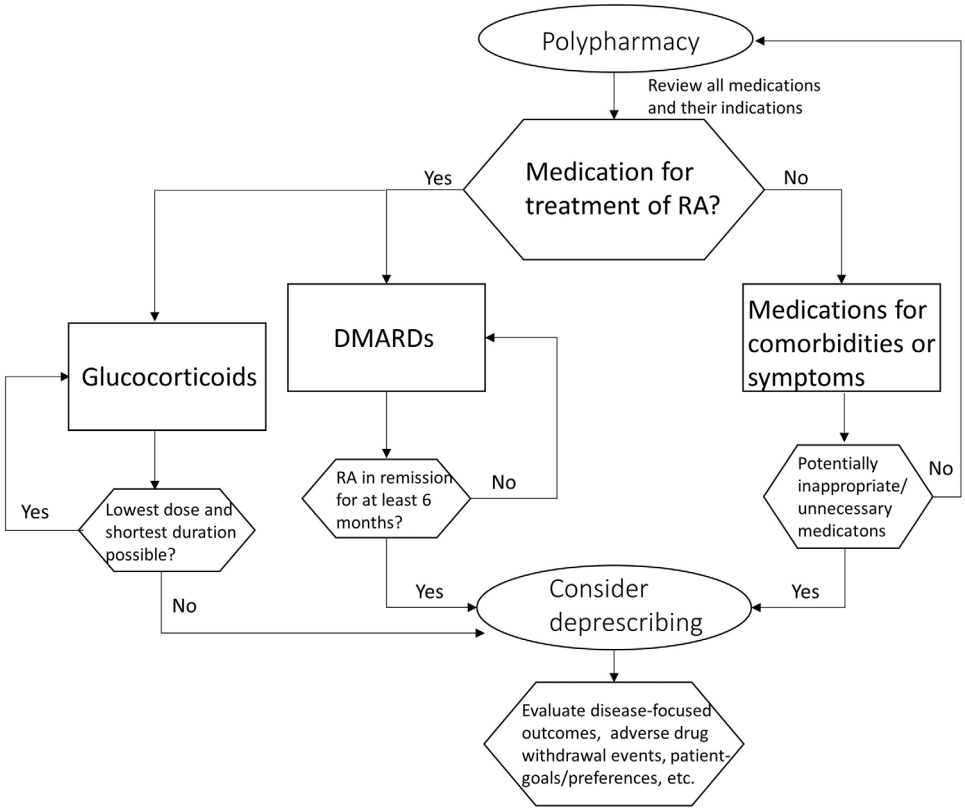


Figure 1. Proposed approach to deprescribing in older adults with RA. DMARD, disease modifying antirheumatic drug; RA, rheumatoid arthritis.

medication use, the National Committee for Quality Assurance updated the 2022 Healthcare Effectiveness Data and Information Set to introduce "deprescribing benzodiazepines in older adults" as a new health care performance measure (62).

Table 1 summarizes several practice improvement tools to support deprescribing of common PIMs. Deprescribing interventions that involve comprehensive medication review, educational interventions, and computerized decision support aids have reduced PIM use among community-living older adults in other fields (63). Although rheumatologists may not be the main prescriber of and/or may be hesitant to make changes to non-DMARD medications, we implore rheumatologists to screen for PIM use in older adults with RMDs given their prevalence and potential detrimental effects, then consider adopting deprescribing practices to optimize medication use and outcomes in our older patients. A coordinated approach with primary care physicians and other interdisciplinary care team members including geriatricians and pharmacists can ensure that PIM deprescribing is evidence-based and adverse drug withdrawal events and other outcomes are appropriately monitored.

Deprescribing medications used for treatment of RMDs in older adults: general concepts, current evidence, and proposed approach. As patients with RMDs age, rheumatologists must continually assess disease activity, disease burden, medication adverse effects, functional status, and patient-identified values and goals for care of RMDs, without making assumptions, as these can change with time and treatment decisions must align with these preferences. Therefore, now is the time to evaluate and understand how deprescribing principles may be tailored to older adults with RMDs. As an illustration of the feasibility of this approach in RMDs, Australia developed an evidence-based guide to deprescribing allopurinol in individuals with low risk of relapse for gout (64).

Although deprescribing, at this time, may not be widely adopted as a concept or terminology in rheumatology, clinical guidelines and studies allude to this approach to medication management, to variable degrees, using terms such as "withdrawing," "tapering," "dose reduction," "interval-increase," or "stopping/cessation/discontinuation." For example, the American College of Rheumatology (ACR) and European League Against Rheumatism clinical guidelines for the treatment of RA include recommendations to taper or discontinue DMARDs in individuals with sustained remission (2,65).

Thoughtful and systematic approaches to treatment initiation for RA in a T2T approach and remission induction for other RMDs such as SLE and anti-neutorphil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) exist. However, evidence-based guidance is lacking on optimal length of maintenance therapy or deprescribing these medications when appropriate, especially in older adults. This is despite findings that 30% to 80% of well-

controlled patients with RA can taper DMARDs with favorable outcomes and this approach is cost-effective (66,67). In addition, more recent evidence suggests that mycophenolate mofetil may be tapered if lupus nephritis is in remission for more than 18 months without increased risk of flare (68). Importantly, studies suggest that most patients are willing to try reducing RA medication if suggested by their rheumatologist and if they have timely and adequate access to care (69–72).

Deprescribing DMARDs in RA. The introduction and rapid expansion of available DMARDs—especially biologics, including TNF inhibitors (TNFis)—has revolutionized RA treatment; however, their use is also costly and associated with increased risk of serious infection, malignancy, and other adverse effects (11,12,73–76). With shifts in treatment paradigm toward a T2T approach that advocates for early aggressive initiation of DMARDs, disease remission became an attainable goal, and thereafter questions rose regarding the optimal duration and/or intensity of treatment after long-standing remission became paramount. To this end, in the 2021 guidelines, ACR identified "when, which, and how should DMARDs be tapered/discontinued" as a key clinical question requiring future research (1).

Two review articles summarize evidence generated in the past few decades to support and guide deprescribing DMARDs in RA. A systematic review by Curtis et al focusing on TNFi discontinuation identified nine studies, and a review article by Schett et al evaluating tapering or discontinuing DMARDs (including non-TNFi biologics) identified 28 studies (66,67). In sum, excluding overlap, the two reviews identified 30 studies that included observational studies, *post hoc* analyses of data from clinical trials, or RCTs that were heterogenous in their eligibility criteria, DMARD of interest, sample size, mode of deprescribing (stop vs. taper), and outcomes. Overall, about one third to half of patients with RA were able to taper biologic DMARDs for more than 1 year, and in the event of a flare, most were able to restore remission with reinitiation of treatment (66,67). Lower rates of relapse were associated with rapid response to initial treatment, sustained/deep remission prior to taper, shorter RA disease duration, seronegativity, and male gender. More recent RCTs including the Optimizing TNF Tapering in RA (OPTTIRA) trial (77) and tapering toward DMARD-free Remission in Established RA (TARA) trial (78) add to the dearth of evidence regarding the feasibility and cost-effectiveness of deprescribing DMARDs. Interestingly, many of the studies on deprescribing in RA originate from Europe, which raises questions regarding the differential attention to this topic and feasibility of implementing this approach in the United States given the vastly different health care culture, policy, and delivery systems.

Deprescribing GCs in RA. GCs are commonly prescribed and effective in the management of RA; however, their safety and utility long term (≥3 months), even at a low dose, has been widely debated. Among patients with RA, 30% to 65% are on long-term GCs and higher rates are common in older adults and those with higher comorbidity (38). In a large observational study, GC use was associated with a dose-dependent increase in the risk of serious infection, even at doses of 5 mg or less per day (79). One study suggests a favorable benefit–harm ratio with low-dose GC; however, excluded older adults and those with comorbidities likely to be more harmed by the negative effects of GCs (80). Along with dose, duration of GC exposure is associated with adverse risk profiles and increased rates of diabetes, osteoporosis, thrombotic stroke or myocardial infarction, and death (81). In addition, GCs are listed in the Beers Criteria to carry high risk of gastrointestinal bleeding or peptic ulcer if used in conjunction with NSAIDs (30), another medication commonly used by individuals with RA. Therefore, updated national and international treatment guidelines strongly discourage long-term GC use and strongly recommend their discontinuation in well-controlled RA (2,65).

Despite the potential benefit of deprescribing, tapering and/or discontinuing, GCs to avoid long-term use, contemporary data to inform development of evidence-based and patient-centered approaches to GC deprescribing are limited. Wallace et al evaluated 16 studies focusing on oral GC tapering, 11 of which were clinical trials identified since 2008, and five were previously found to focus on this topic between 1972 and 2011 (82). The authors concluded that current evidence is insufficient to develop data-driven protocols for GC tapering because only one study evaluated GC withdrawal symptoms and none directly compared the efficacy of different GC tapering regimens. In 2020, Burmester et al published the Steroid EliMination in Rheumatoid Arthritis (SEMIRA) trial (NCT012573012), a multi-center double-blind randomized controlled trial involving 259 participants (83). In this study, adults with RA and stable low disease activity on tocilizumab and long-term GCs were randomized to either continue or slowly taper 5 mg per day of prednisone and observed during 24-week study period. Two thirds were able to taper GCs without flare or evidence of adrenal insufficiency, demonstrating the efficacy and feasibility of deprescribing GCs in patients with RA with long-term use. However, this study was limited mostly to middle-aged adults (mean age, 54.4; SD, 13.4) and did not monitor for adverse drug withdrawal events related to GCs. There are several studies on GC tapering registered on clinicaltrials.gov, and additional data to inform deprescribing regimens are expected in the coming years.

Deprescribing in multimorbid patient with RMDs: an example with concurrent diagnosis of RA and cancer. Multimorbidity, which often precludes the safe and effective use of medications, contributes to the challenges of prescribing and deprescribing in older adults. Compared to the general population, individuals with RA have a higher risk of cancer (84,85), particularly of lymphoma and lung cancer. Older adults with cancer

often have an even higher prevalence of comorbidity than an age-matched control group without cancer (86). In a study by Williams et al, 92% reported one or more comorbid condition and a mean of 2.7 conditions (range 0–10), with arthritis being the most common (52%) (87). Thus, rheumatologists are bound to see a growing number of complex, older adults with RMDs and diagnosis of cancer. In this section, we highlight a clinical case with concurrent diagnosis of RMDs and cancer that provides a unique opportunity to consider the complexity of deprescribing in patients with multimorbidity.

A common clinical scenario: Let us consider decision making regarding the management of RA with persistent low disease activity on methotrexate, hydroxychloroquine, and adalimumab in a 76-year-old man with longstanding history of hypertension, diabetes, osteopenia, and a new diagnosis of lung cancer. He expressed interest in reducing DMARDs for the last three visits. Nearly all trials for RA exclude subjects with active cancer (and similarly, cancer trials often exclude those with active RA). Therefore, clinical practice guidelines that center around a single disease state and focus on disease-specific outcomes, based on data derived from middle-aged adults with exclusion of multimorbid older adults commonly encountered in routine care, have limited utility for guiding management in these situations.

In our clinical scenario, physician(s) and patients need to engage in shared decision making to consider goals of care, the benefit–harm ratio of DMARDs, therapeutic options for the newly diagnosed lung cancer, the potential for drug–drug interaction and drug–disease interactions with the diagnosis of lung cancer, RA, and other chronic conditions, and what are the potential trade-offs (such as RA disease flares) the patient is willing to consider. In essence, it is important to pause and ask the following question that Tinetti et al (88) pose for delivery of patient-centered care: "Is the potential benefit of the medication worth the potential harm and burden and is it likely to result in the outcomes that matter to the patient?" To not only ask, but ultimately, address/resolve this question effectively, rheumatologists need to learn about and adopt geriatric principles to provide high quality patient-centered care and optimize safe and effective medication use for older adults with RMDs and competing multimorbidity. Moreover, this prompts rheumatologists to leverage expertise from other specialties to build interprofessional relationships and interdisciplinary teams with strong communication to improve quality of care for older adults (89) and optimize management through collaborative knowledge sharing in the face of little to suboptimal evidence-based guidelines in this population. This will allow delivery of patient-centered care where the preferences and values of an individual patient are upheld, and the patient is treated holistically as opposed to approaching each condition or disease in isolation.

Future directions. The USDeN identified the following four high-priority areas for deprescribing research: 1) comparing the relative benefits of deprescribing interventions and patient population targets, 2) identifying and defining measures that can assess deprescribing using routinely collected clinical data, 3) harmonizing electronic health record data to build infrastructure for future multi-site pragmatic deprescribing trials, and 4) developing tools for deprescribing communication to promote shared decision making. All of these areas are ripe for further development and investigation within rheumatology.

Future work is needed in rheumatology to develop evidence-based deprescribing protocols and monitoring practices that are patient centered and goal concordant. For example, future work in RA should consider the optimal duration of remission prior to deprescribing, the comparative efficacy and cost-effectiveness of various deprescribing regimens (eg, gradual vs. abrupt, with or without steroid bridging), and the utility of pharmacogenetic/biomarkers and (advanced) radiographic studies to define eligibility criteria; should personalize the approach and/or provide monitoring; and should generate quality measures for adverse drug withdrawal–related outcomes. In addition, researchers should focus on engaging stakeholders (including patients, caregivers, and the health care team) to understand facilitators and barriers to the implementation of deprescribing, providing patient- and provider-facing education, and designing innovative care delivery models in order to ultimately reduce polypharmacy and optimize medication use in complex older adults with RMDs.

We should be cautious, however, so that deprescribing does not result in the undertreatment of older adults with RMDs. Instead, deprescribing can add value to the care of older adults with competing multimorbidity and greater burden of polypharmacy as this approach includes continuous and frequent assessment of benefit–harm ratios and allows for dynamic and tailored approaches to treatment. Incorporation of deprescribing within the rheumatology field would be a paradigm shift for RA treatment from T2T toward remission induction followed by remission maintenance (similar to AAV), and possibly drug-holiday or drug-free remission (90).

CONCLUSIONS

As the rheumatology patient population ages globally, it is imperative to understand the burden of polypharmacy and adopt good prescribing practices to improve safe and effective medication use in older adults. As general medical practice and other medical specialties have done in recent years, we implore rheumatologists to consider the potential of deprescribing to reduce PIM use and optimize therapeutic approaches for older adults with RMDs (Figure 1). Deprescribing involves behavioral change and embodies the geriatric principle of 5Ms to consider older adults as a whole person, living with competing multimorbid conditions, advanced illness, and/or complicated biopsychosocial needs, and shifting priorities/goals of care. We encourage the

rheumatology community to learn, adapt (when necessary), and implement geriatric and deprescribing principles, as we move toward becoming an age-friendly health care specialty.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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