Less is More: Deprescribing Medications in Older Adults with Kidney Disease: A Review
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Running Header: Deprescribing in older adults with kidney disease
Abstract
Due to both age and impaired kidney function, older adults with kidney disease are at increased risk of medication-related problems and related hospitalizations. One proactive approach to minimize this risk is deprescribing. Deprescribing refers to the systematic process of reducing or stopping a medication. Aside from preventing harm, deprescribing can potentially optimize patients’ quality of life by aligning medications with their goals of care. For some patients, deprescribing could involve less aggressive management of their diabetes and/or hypertension. In other instances, deprescribing targets may include potentially inappropriate medications that carry greater risk of harm than benefit in older adults, medications that have questionable efficacy, including medications that have varying efficacy by degree of kidney function, and that increase medication regimen complexity. We include a guide for clinicians to utilize in deprescribing, the List, Evaluate, Shared Decision-Making, Support (LESS) framework. The LESS framework provides key considerations at each step of the deprescribing process that can be tailored for the medications and context of individual patients. Patient characteristics or clinical events that warrant consideration of deprescribing include limited life expectancy, cognitive impairment, and health status changes, such as dialysis initiation or recent hospitalization. We acknowledge patient, clinician, and system-level challenges to the deprescribing process. These include patient hesitancy and challenges to discussing goals of care, clinician time constraints and a lack of evidence-based guidelines, as well as system-level challenges of interoperable electronic health records and limited incentives for deprescribing. However, novel evidence-based tools designed to facilitate deprescribing and future evidence on effectiveness of deprescribing could help mitigate these barriers. This review provides foundational knowledge on deprescribing as an emerging component of clinical practice and research within nephrology.

Introduction
More than half of older adults with kidney disease have at least one medication that is either renally inappropriate or potentially inappropriate for their age\(^1\). The combination of older age and kidney disease, compared to either characteristic alone, confer heightened vulnerability to medication-related problems\(^2\). Yet, medication-related harms can be prevented through improvements in the quality of medication decision-making for older adults with kidney disease.

Several factors contribute to medication-related problems in older adults with kidney disease. Older age can cause alterations in medication pharmacokinetics and/or pharmacodynamics, compounding the impact of declining or minimal kidney function on clearance of specific medications. Underlying reasons for these alterations include decreased muscle mass, reduced kidney mass and perfusion, and malnutrition\(^3\). As a result, medication risk/benefit profiles differ in older adults because some medications carry greater risk of harm than benefit due to increased risk of geriatric syndromes, including cognitive impairment or falls\(^4,5\). In addition, the benefits or efficacy of some medications may be equivocal because of limited life expectancy or limited clinical trial data involving older adults. Older adults with kidney disease also often have multiple clinicians, subsequently more medication prescribers, a high prevalence of polypharmacy, and a higher risk of medication-related problems\(^6,7\). Increased prevalence of care transitions and clinician changes among older adults, including hospitalizations and dialysis initiation, may predispose patients to prescribing cascades if they are executed without careful medication review\(^8\). Given the accelerated aging inherent to kidney disease, it is important to acknowledge these factors may also exist in young patients with kidney disease\(^9\).

While an essential approach to prevent medication-related problems is to consider risks and benefits at medication initiation, it is also important to consider deprescribing medications that may carry new risk or limited efficacy with increasing age and/or declining kidney function. Deprescribing is the process of reducing or stopping a medication which can potentially
improve clinical outcomes in older adults with kidney disease\textsuperscript{7, 10, 11}. While deprescribing is typically done in reaction to a preventable medication-related problem (e.g., reducing insulin after hypoglycemia), proactive deprescribing is routine for nephrology practices when doses of medications are decreased as kidney function declines. However, proactive deprescribing of medications not primarily cleared by the kidneys should also be considered\textsuperscript{12}. Formally, deprescribing involves a systematic process of medication reconciliation, medication review, shared decision-making, followed by implementation and monitoring\textsuperscript{13}.

Deprescribing leads to lower use and/or prescribing of medications that carry greater risk of harm than benefit in older adults (e.g., sedative-hypnotics, first-generation antihistamines).\textsuperscript{14-17} Deprescribing interventions are varied in methodology (e.g., clinician and/or patient education, clinician-led deprescribing, pharmacist medication review and recommendations), setting (e.g., hospital, nursing home, primary care), and approach (e.g., single or multiple medication targets). This variation in methodology and rigor has limited generalizability of existing evidence.\textsuperscript{18, 19} However, meta-analyses suggest deprescribing involving medication review (often pharmacist-led) may yield a reduction in all-cause mortality (26\% relative risk reduction) among community-dwelling older adults and falls among nursing home residents.\textsuperscript{20, 21} Other patient benefits of deprescribing include improved adherence, improved quality of life, and lower financial burden\textsuperscript{22}. Older adults with polypharmacy acknowledge their medication burden and would be willing to attempt deprescribing at least one medication if their physician said it was possible\textsuperscript{23}. Patients requiring dialysis also report satisfaction in a deprescribing quality improvement program\textsuperscript{24}. This evidence demonstrates the potential benefit of deprescribing for older adults with kidney disease.

This literature review attempts to promote integration of deprescribing into routine care in chronic kidney disease (CKD) and dialysis clinics by delineating three overarching areas for consideration of deprescribing: 1) less intensive management of exemplar chronic conditions (diabetes and hypertension), 2) less inappropriate prescribing, and 3) less medication regimen
complexity. Then, this review provides a deprescribing framework to facilitate clinical encounters. Last, we address common deprescribing challenges and recommendations for future research.

**Less Intensive Management of Diabetes and Hypertension**

Glycemic control is standard of care for CKD management. Yet intensive glycemic control, defined as therapy yielding hypoglycemic events and/or Hemoglobin A1c (A1C) <6%, can be harmful in older adults with kidney disease. The risk of sarcopenia and frailty also increases in older adults with diabetes and CKD resulting in reduced insulin clearance which may be particularly concerning because older adults may have less hypoglycemic awareness. Hypoglycemic events are independently a cause for substantial concern because of their severe sequelae including dizziness, slurred speech, seizure, cognitive decline, functional decline, and confusion, or more acute events increasing the risk of cardiac ischemia or arrythmias. Overtreatment of diabetes has also been linked to increased short and long-term mortality, fractures/head injuries, and cognitive impairment, as well as increased health care utilization and expenditures. For example, in a study of older adults aged ≥75 years treated with at least one antihyperglycemic agent, there was a high prevalence of intensive control (A1C <7), and an increased risk of emergency department visits/hospitalizations or death within 30 days of reaching control using high risk agents (e.g., insulin, or specific sulfonylureas). Furthermore, the risk of hypoglycemia increases with worsening eGFR stage and use of antihyperglycemic medications increases the risk approximately 40 times at each eGFR stage (compared to non-users).

The A1C target of <7 was established from studies including individuals aged <65 years, so clear guidance regarding appropriate A1C targets is lacking for older adults with kidney disease. However, A1C targets in the <8% range may be considered among frail individuals.
and those with limited lifespan, propensity for hypoglycemic events, and limited resources\textsuperscript{25}. More specifically, the American Diabetes Association currently recommends a HbA\textsubscript{1c} <8.0\% for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and comorbid conditions, such as CKD\textsuperscript{32}. Considering these recommendations, we suggest clinicians balance the importance of avoiding hypoglycemic events associated with intensive treatment with avoidance of severe hyperglycemia which can cause negative sequelae including dehydration, polyuria, and predisposition for urinary infections and cardiovascular events\textsuperscript{25}.

While CKD guidelines support a systolic blood pressure <120mmHg\textsuperscript{33}, this goal may not be prudent for older adults with CKD. This intensive blood pressure target was derived from the Systolic Blood Pressure Intervention Trial (SPRINT) which demonstrated reduced cardiovascular events and mortality benefit. However, evidence that this blood pressure target slows kidney disease progression is lacking, thus making its universal applicability to older adults with CKD unclear\textsuperscript{34, 35}. Furthermore, SPRINT excluded older adults having difficulty with physical and/or cognitive function (e.g., nursing home residents, individuals with dementia)\textsuperscript{34}. Thus, the study is not generalizable to a sizable proportion of the older adults with CKD in which these conditions are common. In addition to a lack of clear efficacy, there is risk of harm from intensive blood pressure management. Both hypotension and addition of antihypertensive agents increases older adults’ risk for falls, and related fractures and brain injury\textsuperscript{36}. Addition of antihypertensive agents contributes to medication burden, which can impact a patient’s quality of life\textsuperscript{37}. A clinical trial demonstrated no difference in adverse events between patients who had (versus those who did not) antihypertensives deprescribed, providing reassurance for deprescribing antihypertensives in older adults with moderate CKD\textsuperscript{38}.

**Less Inappropriate Prescribing of Medications**
Older adults with kidney disease may be inappropriately prescribed medications that: 1) have more potential risk of harm than benefit and/or 2) have questionable efficacy. Continued use of medications in either category as patients age and/or kidney disease progresses can lead to preventable adverse events. Care for patients with kidney disease tends to focus on deprescribing medications with greater risk than benefit due to impaired kidney function. In addition, clinicians should consider deprescribing potentially inappropriate medications (PIMs), or medications that carry substantial risk in older adults. The American Geriatrics Society developed the Beers criteria which provides guidance regarding a list of PIMs. Similar comprehensive guides with specific criteria exist worldwide. PIMs represent a broad range of medication categories (e.g., central nervous system (CNS)-active, anti-thrombotics, endocrine, cardiovascular). PIMs have been associated with falls, confusion, death, and hospitalizations in older community dwelling populations. PIMs use in older adults is also associated with higher healthcare utilization, including outpatient visits and emergency room visits. Notably, more than half of older adults with CKD have at least one PIM. Rates of PIM prescribing among older adults with advanced CKD is at least three times the prescribing rates of medications with primarily renal clearance. Among older adults receiving dialysis, nearly half have a PIM prescription presumably used for symptoms associated with end-stage kidney disease (ESKD), such as anxiety, muscle cramps, or pain (e.g., benzodiazepines, muscle relaxants, opioids, gabapentinoids). Some epidemiologic studies of specific PIMs, predominantly CNS-active medications, demonstrate increased risk of harm, such as fall, fracture or altered mental status, in patients with kidney disease. Additionally, PIMs carry critical theoretical risks of adverse events. For example, a patient receiving a CNS-active medication could experience lethargy leading to falls, confusion, long-term cognitive impairment, or motor vehicle crashes.
In contrast to PIMs, medications with questionable efficacy may not carry demonstrable benefit for older adults with kidney disease as commonly prescribed medications have been understudied in older adults\textsuperscript{50}. As kidney function declines, the efficacy of some medications also declines. For example, dialysis initiation can lead to loss of efficacy of diuretics over time. Medications can develop questionable efficacy because of health status changes. Patient with declining life expectancy (≤6 months) should have their medications reviewed for questionable efficacy (e.g., statins and other lipid lowering medications).\textsuperscript{51 52} Continuation of dual antiplatelet therapy beyond six or 12 months may need to be considered on an individual basis given limited evidence for extended therapy in this population\textsuperscript{53}. Medications with questionable efficacy carry limited benefit, and could become burdensome and impair quality of life. Thus, if polypharmacy is concomitant with substantial pill burden or side effects, medications with little benefit should be considered for deprescribing\textsuperscript{54}. Our clinical vignette illustrates medication targets for less inappropriate prescribing (Figure 1).\textsuperscript{51, 55, 56}

**Less Complexity in Medication Regimens**

Individuals with advanced CKD and ESKD receiving kidney replacement therapies have a high burden of medications in part due to the co-morbid conditions including hypertension, diabetes, and cardiovascular disease. For example, individuals requiring dialysis take approximately 10-12 prescribed and over-the-counter medications and nearly 19 pills per day\textsuperscript{57-60}. Adding to the volume of medications, medication regimen complexity can increase based on directions for use (e.g., before or after dialysis sessions), dosing frequencies (e.g., including at varying times of the day or after vs. with meals), as well as complex dosage formulations that may be more difficult to use (e.g., injectables). These elements of complexity are included in the 65-item validated Medication Regimen Complexity Index (MRCI).\textsuperscript{61} Higher MRCI scores have been linked to medication-related problems, poor medication adherence, mortality, and hospital
readmissions. When the MRCI is applied to individuals with kidney failure, regimen complexity can increase with transplant or dialysis modality change. Individuals on home hemodialysis (HHD) take fewer medications due to improved blood pressure and lower serum phosphorus, but medication regimen complexity is increased due to the need for injections at home (e.g., erythropoietin stimulating agent) and the need to manage dialysate for HHD. Changes in complexity can be especially critical among older adults with kidney disease for whom cognitive impairment is prevalent but poorly recognized, or for whom worsening dexterity may impair injection delivery or opening pill bottles. While the MRCI is not practical for routine clinical use, its elements provide insight for clinicians on how to assess for and reduce medication complexity. Clinicians should be cognizant of medication changes impacting complexity and consider ways to reduce complexity when warranted (e.g., considering combination pills, reducing the frequency of medications, eliminating medications that are difficult to administer when possible). Although polypills have been suggested as a strategy to decrease pill burden, regimen complexity, and adherence concerns, few studies have examined this approach in older adults with kidney disease. Further this strategy is limited by the difficulty of adjusting doses with kidney disease progression or occurrence of side effects with an individual medication within the polypill.

The List, Evaluate, Shared Decision-Making, Support (LESS) Framework for Deprescribing

To identify opportunities for deprescribing, clinicians can use the List, Evaluate, Shared Decision-Making, Support (LESS) framework (Figure 2). The LESS framework acknowledges deprescribing should be individualized to a given patient. Therefore, clinicians should start with an accurate, current medication list through a structured medication reconciliation process.
Next, clinicians should evaluate the medication list using a structured process (i.e., medication review) identifying medications having high risk-to-benefit profile, limited efficacy, those no longer indicated, and regimens too complex for safe use (Examples in Table 1). In some instances, there is insufficient evidence on a medication’s risk in older adults with kidney disease. Clinicians can extrapolate from evidence obtained from cohort studies conducted in the general older adult population. This extrapolation is reasonable as individuals with impaired kidney function may have a narrower therapeutic window and/or uremic toxins that may impact hepatic drug metabolism. Clinicians can also rely on the patient’s preferences and goals of care to discern if a specific medication with unclear risks should be considered for deprescribing.

Clinicians should also evaluate for specific patient characteristics including presence of limited life expectancy and/or characteristics associated with increased risk of medication-related problems, such as frailty, cognitive impairment or mobility impairment. Assessments identifying patients with limited life expectancy include the surprise question (i.e., “Would I be surprised if this patient died in the next year?”), a Karnofsky Performance status score, and/or activities of daily living assessment. Clinicians may also prioritize patients with recent care transitions, including dialysis initiation, hospitalization, or nursing home admission.

Once medication(s) eligible for deprescribing are identified, shared decision-making is a critical next step. The information sharing between patients and clinicians would include discussions about the risks, benefits, and alternatives of the medications considered for deprescribing, followed by collaborative decision-making. The decision-making discussion can mirror an existing communication framework used for dialysis decision-making: setup, perceptions and perspectives, invitation, recommendation, empathize, summarize and strategize (SPIRES). SPIRES allows clinicians to formally introduce the decision to be made, to
understand “their worries and hopes” related to deprescribing a medication, and develop an individualized plan. The shared decision making discussion can be further enhanced through incorporating five social-contextual factors: 1) clinical, 2) psychological, 3) social, 4) financial, and 5) physical (Table 2). Addressing these factors provides more context for patients’ medication use and goals of care. With this, clinicians can discern whether deprescribing is consistent with patient social contexts and preferences, and how to prioritize medications for deprescribing. Decision-aids may be incorporated to increase the quality and efficiency of decision-making.

The final step is to deprescribe the medication(s) and provide adequate support to ensure shared decision plan is executed. Support is demonstrated through providing patient-friendly instructions for medication tapering, education about potential withdrawal symptoms, a plan for alternative medications, and/or non-pharmacological approaches to symptom management. Similar to time-limited dialysis trials, deprescribing is time-limited as a patient who does not achieve explicit goal during a deprescribing trial (e.g., lower dose provides symptom relief) can resume the original dose. Therefore, patient support includes close monitoring and resuming medication if intolerance occurs. Further, a clinician should notify the patient’s pharmacy and other clinicians to ensure medication(s) not be refilled or prescribed again. Table 3 includes deprescribing resources at the point of care, which clinicians and patients can use to evaluate and target medications for deprescribing, engage in shared decision-making, and provide deprescribing support. While most resources are not tailored for older adults with kidney disease, these tools can be extrapolated to this population.

**Challenges of Deprescribing**

Despite its merits, deprescribing may be challenged by patients and their caregivers, the care team, and system level barriers that include fragmentation of care. In a systematic
review, major patient-level barriers to deprescribing included lack of support/time/guidance from clinicians regarding the deprescribing decision, feeling a sense of pressure to continue taking the medication as prescribed, prior negative experiences from deprescribing, and generalized worries regarding coping and other implications of deprescribing (including fear of withdrawal or symptom relapse)\(^8\). Patients also may have concerns about changing a medication used long-term, discussing their goals of care and life expectancy, and/or asking their clinician questions about the decision to deprescribe.

Clinician-level challenges include limited understanding regarding deprescribing and PIMs, inertia to act based in low perceived value of de-prescribing, low self-efficacy, and low feasibility of deprescribing\(^8\). Clinician barriers also include managing alternate goals during the patient encounter (e.g., achieving glycemic goals to meet a metric or guideline), challenges communicating with other clinical team members, inadequate time and training on how to approach deprescribing, and a lack of clear evidence-based guidelines\(^8,8\). Conflicts between the role of the pharmacist, primary care physician, and specialists may also impair deprescribing --- and this may be especially challenging if there is not an interoperable electronic health record (EHR) for communicating questions or concerns regarding medications\(^8,8\).

System-level challenges include 1) limited resources (e.g., time and administrative support) 2) the absence of interoperable EHRs, and 3) the absence of policies promoting individualized medication management. With performance metrics not accounting for goals of care and tailored shared decision-making among older adults with kidney disease (e.g., guidelines for tight BP and glucose control), clinicians are more likely to make decisions poorly individualized to the needs, risks, and benefits for patients\(^8,8\).

Despite these barriers, several potential solutions exist. At the patient level, shared decision-making tools may aid discussions about the appropriateness and benefits of deprescribing and enhance buy-in. Patients and their caregivers should be empowered through
educational efforts to discuss concerns specific to medications identified for deprescribing. In clinics, there can be a structured approach to identifying patients eligible for deprescribing with clearly-defined roles for each clinician involved (nurse, physician, pharmacist). At a system level, increasing financial incentives to enhance multidisciplinary collaboration (e.g., with specific roles and reimbursement incentives for community pharmacists and clinicians) for deprescribing efforts and increasing the interoperability of EHRs may reduce barriers. This should be coupled with renewed performance metrics that incentivize 1) tailored deprescribing (versus inappropriately penalizing deprescribing statins and other agents with uncertain efficacy) and 2) medication review at key care transitions.

**Recommended areas for research**

Nephrology clinicians need more evidence to guide deprescribing efforts; therefore, there is a need for additional pharmacoepidemiologic studies and consensus methods to identify potentially harmful medications and how to deprescribe them. Clinical trials are needed to assess the effect of deprescribing on hospitalizations and patient-reported outcomes, such as health-related quality of life, in patients across the continuum of kidney disease.\(^8\) Last, there is a need for observational studies to identify patient factors that may increase risk associated with specific medications.

**Conclusion**

With the growing number of older adults with kidney disease, the prevalence of medication-related problems is likely to increase. These medication-related problems are not limited to altered kidney clearance. Medication-related problems can also develop from intensive management of chronic conditions, use of PIMs, and patient challenges following complex medication regimens. Deprescribing could improve quality of life among older adults with kidney disease while minimizing pill burden and risk of harm, including hospitalizations. We are conducting studies to inform best practices to overcome challenges to deprescribing,
identify risk attributable to certain medications in older adults with kidney disease, and
demonstrate efficacy of deprescribing in this population. While additional research is needed,
this review provides a framework and resources for nephrology clinicians to proactively consider
deprescribing in practice.
Disclosures

D. Mohottige reports the following: Ownership Interest: My partner owns minimal stocks in Gilead and Pfizer totaling <$5,000; Other Interests/Relationships: NKF Health Equity Advisory Committee member. R. Hall reports the following: Consultancy Agreements: United Health Group, Bayer, Reata Pharmaceuticals, Tavere Pharmaceuticals; Scientific Advisor or Membership: CJASN Editorial Board, Journal of American Geriatrics Society Editorial Board. The remaining author has nothing to disclose.

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Author Contributions

D. Mohottige: Conceptualization; Methodology; Writing - original draft; Writing - review and editing

H. Manley: Conceptualization; Methodology; Writing - review and editing

R. Hall: Conceptualization; Funding acquisition; Methodology; Writing - original draft; Writing - review and editing
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<table>
<thead>
<tr>
<th>Deprescribing principle</th>
<th>Medication</th>
<th>Considerations in non-dialysis patients</th>
<th>Considerations in dialysis</th>
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<tbody>
<tr>
<td>Deprescribe medication with risk exceeds desired benefit.</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; gen sulfonylurea - glyburide</td>
<td>No specific restrictions</td>
<td>Avoid due to higher risk of hypoglycemic events compared to other anti-glycemic agents&lt;sup&gt;a&lt;/sup&gt;,&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>dabigatran</td>
<td>No specific data&lt;sup&gt;c&lt;/sup&gt;</td>
<td>bleed risk increases with GFR decline; safer agent available (Apixaban)&lt;sup&gt;d&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
<td>metformin</td>
<td>Discontinue use of metformin as it is excreted by the kidneys, and accumulation with reduced kidney function may increase risk of lactic acidosis&lt;sup&gt;f&lt;/sup&gt; when eGFR is &lt;30 per FDA standards&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Contraindicated in dialysis</td>
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<td>Baclofen and other muscle relaxants (e.g., dantrolene, metaxalol, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol, tizanidine, or orphenadrine)</td>
<td>Baclofen use is associated with encephalopathy among older adults with CKD at high doses (&gt; or equal to 20 mg per day).&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Muscle relaxant use is common in ESKD HD patients and associated with encephalopathy and falls.&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
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<td></td>
<td></td>
<td>In older adults with CKD (eGFR&lt; 60), baclofen prescriptions at 20 mg or more per day were associated with higher risk of</td>
<td>Baclofen should be avoided in individuals on dialysis because of the risk of hospitalization and encephalopathy.&lt;sup&gt;j&lt;/sup&gt;</td>
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<sup>a</sup> Ref. 88, 89

<sup>b</sup> Ref. 90

<sup>c</sup> Ref. 91, 92

<sup>d</sup> Ref. 93

<sup>e</sup> Ref. 94

<sup>f</sup> Ref. 95

<sup>g</sup> Ref. 96

<sup>h</sup> Ref. 97
<table>
<thead>
<tr>
<th>Opiate (e.g., hydrocodone, oxycodone, tramadol, codeine, hydromorphone, fentanyl, methadone, meperidine, and morphine)</th>
<th>Among individuals on hemodialysis, all opiate agents were associated with a significantly higher hazard of altered mental status. Several agents were associated with a higher hazard of falls, and fracture in a dose dependent manner, and risks were present even at lower dosing and for agents recommended for use in dialysis.</th>
<th>Opiate use was associated with 50% GFR reduction and kidney failure/hospitalization and pre-kidney failure death vs. NSAID among individuals with CKD.</th>
</tr>
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<tbody>
<tr>
<td>Pregabalin and gabapentin</td>
<td>Data unavailable except for limited data showing effective use for chronic uremic pruritis.</td>
<td>Among individuals with EKSD on hemodialysis, Gabapentin was associated with higher hazards of altered mental status, fall, and fracture, respectively, in the highest dose category; Pregabalin was associated with up to 51% and 68% higher hazards of altered mental status and fall, respectively.</td>
</tr>
<tr>
<td>Medication</td>
<td>Available Data</td>
<td>Notes</td>
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<td>------------------------------------</td>
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<td>-----------------------------------------------------------------------</td>
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<tr>
<td>Benzodiazepines</td>
<td>Limited data</td>
<td>Co-dispensing opioids and short acting benzo is common among individuals on dialysis and associated with a higher risk of death.</td>
</tr>
<tr>
<td>Sedative hypnotics (zolpidem)</td>
<td>Limited data</td>
<td>Individuals initiating Zolpidem had an increased risk of fall related fractures vs. trazodone among individuals on maintenance hemodialysis</td>
</tr>
<tr>
<td>Deprescribe medication that requires significant kidney function for efficacy</td>
<td>Rapidly evolving guidelines suggest SGLT2 inhibition for patients with T2DM and eGFR as low as 30 mL/min/1.73 m², particularly if severely increased albuminuria is present, SGLT2 inhibitor withdrawal is not required if eGFR decreases to &lt;30 mL/min/1.73 m², as per the CREDENCE protocol. If DAPA-CKD was stopped early for overwhelming efficacy, the eGFR cutoff could be reduced to 25 mL/min/1.73 m².</td>
<td></td>
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<tr>
<td>SGLT2 inhibitors</td>
<td>Discontinue use of SGLT2 inhibitors as their mechanism of action requires that they be filtered from the blood through the glomerulus to exhibit their inhibitory effects exclusively on the extracellular side of the proximal tubule plasma membrane.</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Limited data</td>
<td>Nitrofurantoin primarily renally excreted, and</td>
</tr>
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Deprescribe medication demonstrated to have limited or no documented benefit in patient with kidney disease

<table>
<thead>
<tr>
<th>Tramadol Extended Release</th>
<th>Limited data available</th>
<th>Extended-release products are not necessary in ESKD products.¹⁰⁶</th>
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<tbody>
<tr>
<td>fenofibrate</td>
<td>In patients with severe renal impairment (creatinine clearance ([\text{CrCl}] \leq 30 \text{ mL/min})) there was 2.7-fold increase in exposure for fenofibric acid and increased accumulation of fenofibric acid compared to that of healthy subjects.¹⁰⁷</td>
<td>Unclear benefit in dialysis patients¹⁰⁸</td>
</tr>
</tbody>
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¹⁰⁵ relies on urinary concentration to achieve its effect. It may be associated neurotoxicity and life-threatening pulmonary toxicity, it should be avoided in patients on dialysis.

¹⁰⁶ Deprescribe medication demonstrated to have limited or no documented benefit in patient with kidney disease

¹⁰⁷ This table demonstrates key principles to consider during medication review and examples of medications. This table should not be considered a complete list of medications for deprescribing.
Table 2. Socio-contextual factors to consider when deprescribing

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Key components of assessment</th>
<th>Example</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>Assess the complex co-morbid conditions impacting a patient, the risks/benefits of medications used to treat each of these, as well as the adverse drug events exacerbated by specific agents. Identify medication benefits vs. harms and expected time to benefit in the context of diagnosis, and symptom management goals (e.g., decreasing pruritis). Prescribing cascades (e.g., proton pump inhibitor for aspirin use) should also be noted along with medications that have equivocal evidence for benefit including preventive agents like statins etc. Finally, available alternatives should be discussed.</td>
<td>(e.g., understand the role of each medication – and assess its use in the context of patient circumstances – i.e., diuretics in an anuric patient)</td>
</tr>
<tr>
<td>Psychological</td>
<td>Determine anxiety/worry re: medications or conditions that impact deprescribing and assess perceptions and/or knowledge regarding treatments (e.g., perceptions of a need for intensive glucose or blood pressure control, or intensive phosphorous control). Any anxieties or distress that arises from possible discontinuation of certain medications should be addressed, as well as patient-identified prioritization of treatment goals. This includes an understanding of health literacy, cognitive function, goals of care (e.g., relief of symptoms, overall function), decisional self-efficacy etc.</td>
<td>(e.g., prioritizing volume management and dyspnea reduction over phosphorous control; exploring anxieties regarding stroke and other cardiovascular event concerns in individuals with non-indicated long term anticoagulant use)</td>
</tr>
<tr>
<td>Social</td>
<td>Assess caregiver and other loved one’s impact on medication decision-making, which may manifest as gatekeeping– (e.g., concerns by family members regarding discontinuation of certain medications); assess other social support concerns and other social responsibilities (e.g., caring for another family member) which may limit time and opportunities for self-care. Family and other loved ones may need to serve as partners in de-prescribing plans, while centering patient values and priorities in this process.</td>
<td>(e.g., concerns among caregivers that deprescribing agents like sleep aids etc. will increase their caregiving needs)</td>
</tr>
<tr>
<td>Financial</td>
<td>Carefully assess costs of medications in the context of health insurance coverage and access including out of pocket costs for non-prescription medications are important provide reassurance that deprescribing shouldn’t be driven exclusively by cost reduction incentives</td>
<td>(e.g., consider when Tums could be safely substituted for more expensive Phosphorous binders);</td>
</tr>
</tbody>
</table>
Assess frailty, changes in dexterity, vision, cognition, and the challenge of taking certain medications (e.g., those more complex to administer including injectables) is an important consideration among older adults. This also may include considerations of how changes in dexterity or memory may impair the ability to adhere to medications before and after dialysis or meals. (e.g., considering *pre-packaged medications for each day of week)

| Physical |
|-----------------|---------------------|
| Assess frailty, changes in dexterity, vision, cognition, and the challenge of taking certain medications (e.g., those more complex to administer including injectables) is an important consideration among older adults. This also may include considerations of how changes in dexterity or memory may impair the ability to adhere to medications before and after dialysis or meals. (e.g., considering *pre-packaged medications for each day of week) |

*These five determinants of deprescribing were obtained from the deprescribing rainbow, a conceptual framework on the importance of patient context in deprescribing.*
<table>
<thead>
<tr>
<th>Tool</th>
<th>Tool platform and population</th>
<th>Key Components</th>
<th>Website (if available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deprescribing algorithms for patients on hemodialysis&lt;sup&gt;109&lt;/sup&gt;</td>
<td>Designed for individuals on dialysis of all ages</td>
<td>9 medication specific deprescribing algorithms provided for individuals on hemodialysis; these are medication specific and patient centered (e.g., loop diuretics, alpha-1 blockers, statins, benzodiazepines, metoclopramide, and gabapentinoids)</td>
<td></td>
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</table>
| MedStopper<sup>110</sup>                      | Web-based platform to aid clinicians and patients | Provides guidance via an ordered system to prioritize deprescribing based on drug impact on symptoms, future impact on illness, and likelihood of causing harm  
Provides tapering suggestions and guidance regarding withdrawal system                                                                                                           | https://medstopper.com/about.php                           |
| G-MEDSS Goal Directed Medication review electronic decision support system<sup>111</sup> | Older adults Web-based platform | A goal-directed medication review electronic decision support tool which identifies patient’s specific deprescribing report based on goals of care attitudes, and drug burden  
Access a goals of care management tool (videos and guide) to engage in shared decision-making regarding goals and priorities  
Embeds the drug burden index and the revised patients’ attitudes toward deprescribing questionnaire                                                                 | https://gmedss.com/landing                                  |
| Medsafer                                       | Older patients                | An electronic deprescribing tool to improve safety  
Provides personalized screening of history and meds; guides physicians and pharmacists in safe and successful deprescribing using criteria to identify PIMS in hospitalized older adults  
Includes links to educational brochures regarding deprescribing (e.g., opiates, proton pump inhibitors, sedatives, sulfonylurea)                                                                                                                | https://www.medsafer.org/study-protocol-le-protocole-detude |
<p>| Primary health                                 | Older adult                  | Website includes principles of deprescribing and                                                                                              | <a href="https://www.primaryhealth">https://www.primaryhealth</a>                                  |</p>
<table>
<thead>
<tr>
<th>Resource</th>
<th>Patient Group</th>
<th>Description</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIMS Plus</td>
<td>All ages</td>
<td>Website with ability to search by medication to identify medication information for consumers as well as guidance regarding when to avoid use Provides patients a survey to help determine the benefit of a medication review</td>
<td><a href="https://www.pimsplus.org/">https://www.pimsplus.org/</a></td>
</tr>
</tbody>
</table>
Figure 1. Clinical Vignette

Figure 2. List Evaluate Shared Decision-Making Support (LESS) Framework for Deprescribing Process
**Illustrative Case:** A 75-year-old man with CKD Stage 4 has rapid eGFR decline; his daughter and primary caregiver describe that he has had increasing difficulty managing medications. A decade ago, he had a sub-lacunar stroke and has been using a high intensity statin since that time. He is also having increased frequency of falls. For his benign prostatic hypertrophy (BPH) he had been taking terazosin at high doses for a long time; however, he has had some orthostatic symptoms related to this agent. In addition, he has recently had some arthritic pain for which he has started using NSAIDs daily.

**Discussion Points for Specific Medications considered for Deprescribing:**

**Terazosin:** Regarding BPH management, one alternative to discontinuing terazosin would be to consider switching it to tamsulosin as fewer patients experienced dizziness [relative risk (RR) 0.38 95% CI: 0.30, 0.48] and severe hypotension (RR 0.16, 95% CI: 0.04, 0.68) compared to patients taking terazosin.\(^5\)

**NSAIDS:** The NSAID use and risk for worsening kidney function requires consideration of alternative agents (e.g., acetaminophen).

**Statins:** Statins may contribute to fall risk. Statins have a limited benefit among individual with limited life expectancy. A discussion regarding overall goals of care and risk vs. benefits associated with continued use of the high intensity statin is warranted.\(^6\)
<table>
<thead>
<tr>
<th>L</th>
<th>List</th>
<th>Create accurate medication list (medication reconciliation)</th>
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<tbody>
<tr>
<td>E</td>
<td>Evaluate</td>
<td>Review each medication to identify target medications for deprescribing:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medications that are not indicated for the patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medications that carry greater risk of harm than benefit for the patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medications that have questionable efficacy for the patient</td>
</tr>
<tr>
<td>S</td>
<td>Shared Decision-Making</td>
<td>Discuss with patient (and caregiver or other prescribers if indicated):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Information: risk, benefit, and alternative medications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient concerns about deprescribing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Goals of Care</td>
</tr>
<tr>
<td>S</td>
<td>Support</td>
<td>Support patient in implementation of deprescribing:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provide clear instructions to patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Close communication plan to monitor for intolerance to deprescribing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Notify pharmacy and other clinicians about medication change(s)</td>
</tr>
</tbody>
</table>