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Strategies for Reducing Polypharmacy and Other Medication-Related Problems in Chronic Kidney Disease

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ABSTRACT

Medication-related problems are very common in patients with chronic kidney disease (CKD). These problems are often avoidable and can result in detrimental patient consequences and high financial costs. Despite these risks, it is often medically necessary to prescribe multiple medications to treat the comorbid conditions that accompany CKD. In addition, patients' use of nonprescription medications and changes in pharmacokinetic and pharmacodynamic parameters may further contribute to medication-related problems in CKD, including drug interactions and the need for dosage adjustments. A structured medication assessment process is one approach to reducing the risks associated with medication-related problems. This multifaceted process involves a comprehensive medication history interview, structured therapy assessment, and open communication between members of the medical team. A detailed description of this process is provided to aid healthcare providers in addressing this important issue.

Polypharmacy is a nonspecific term that is often used to imply a negative situation involving unnecessary or inappropriate use of medications. Polypharmacy involving unwarranted medications may occur unintentionally in situations involving multiple prescribers who are unaware of the medications prescribed by others, when additional medications are used to treat adverse effects of a primary medication, or with generally suboptimal management of therapy as a whole (1). In addition, the self-use of nonprescription medications and other herbal and vitamin therapies can add multiple products to a regimen (2). In general, patients at greatest risk for problems associated with polypharmacy include the elderly, those with four more recorded diagnoses, five or more medications, four or more prescribers, antihypertensive medication use, male gender, recent hospitalization, those with visual or dexterity impairment, use of multiple pharmacies, and use of nonprescription medications, herbs, or nutritional supplements (3,4). In a study of 3005 older adults, over half reported the combined use of five or more prescription medications, nonprescription medications, or dietary supplements. When analyzing prescription medications alone, 29% used more than five medications (5).

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Although the issue of polypharmacy has been a focus of many reports, it comprises just one aspect of the broader concern of medication-related problems. For purposes of analysis, medication-related problems are generally divided into nine categories, including: (i) lack of treatment for a medical condition (indication without drug therapy); (ii) medication treatment is not warranted (drug without an indication); (iii) suboptimal drug selection (the therapy of choice for this patient and condition is not being used); (iv) subtherapeutic dosage; (v) overdosage; (vi) adverse drug reaction (patient is experiencing signs or symptoms caused by a medication); (vii) drug interaction (negative consequences of a drug–drug, drug–disease, drug-laboratory value, or drug–food interaction); (viii) failure to receive therapy (patient is not receiving the prescribed regimen because of nonadherence, lack of accessibility, or cost); and (ix) suboptimal laboratory monitoring (monitoring of the patients' conditions or medication therapy could be improved) (6,7). While these general groupings have been used to categorize medication-related problems, other issues such as the failure of therapy to meet disease treatment goals and medication record discrepancies may overlap between two or more of these groups and are not as easily categorized.

Inappropriate medication use is associated with detrimental patient consequences and high financial costs. The overuse, underuse, or misuse of medications can lead to adverse drug reactions requiring additional physician office visits or hospitalizations, and can result in deterioration of health status and even death (8). The American Society of Consultant Pharmacists Seniors at Risk report states medication-related problems to be of such large proportions that it is declared a public health

problem (9). Annually, more than 200,000 people die and another 2.2 million people are injured because of medication-related problems (10,11). The costs associated with medication-related problems are currently estimated at over $2 billion per year (9). A closer examination of these costs reveals that in 2000, the cost of managing noninstitutional medication-related problems alone was reported at $177 billion (10). In another analysis, it was estimated that for every $1 spent on medications, about $1.77 is spent managing medication-related problems (10,12).

The risk of adverse drug reactions and errors increases dramatically as the number of medications in a regimen increases (8,13,14). In a recent review, Gallagher et al. reported inappropriate prescribing rates from 21.3% in community-dwelling older adults to 40% in nursing homes (8,15). The Institute of Medicine estimates that on average, a hospitalized patient receives 10 doses of medication per day involving one medication error per day. Nursing home patients are predicted to have an even higher medication error rate (14). In addition, drug interactions can become a serious consequence of polypharmacy when complex regimens involving several drugs are prescribed. Potentially major drug interactions were found in one of 25 older adults, with half of these interactions involving nonprescription medications (5).

Despite these risks, it is clear that complex medication regimens comprised of several medications are usually necessary to treat chronic kidney disease (CKD) and related comorbidities. Patients with CKD require multiple medications to treat the medical conditions that accompany the development of CKD (e.g., diabetes mellitus, hypertension, and preventing CKD progression) as well as the common complications of CKD (e.g., anemia, bone and mineral metabolism disorders, hyperlipidemia, and cardiovascular disease). Other health conditions are often present as well. In a study of medication use in CKD stages 3 through 5 (GFR $\leq$ 60 ml/min), patients with CKD were on average 60.6 $\pm$ 16.0 years of age and were prescribed a mean of 8 $\pm$ 4 medications (16). Patients in stage 5 CKD on dialysis average 12 medications to treat five to six comorbid conditions (12).

Use of the many medications required in CKD demands careful attention to the balance between the need to avoid under treatment of the concomitant conditions associated with CKD while avoiding unnecessary hazards of polypharmacy. The challenge for clinicians is to balance the risk vs. benefit of these multiple medications. Therefore, this paper will explore the issues and consequences of medication-related problems in patients with CKD, examine the role of the pharmacist in preventing and managing medication-related problems, and propose a structured approach to medication therapy review to avoid medication-related problems.

Challenges Associated with Medication Prescribing in CKD

Patients with CKD are medically complex, and the sheer number of medications they require can pose a challenge even to the most experienced prescriber. Adding to this challenge is the difficulty of tracking and managing medications recommended by other prescribers (e.g., specialists) and the nonprescription products that patients may self-administer. Routine medical histories may not always discover the patients' use of nonprescription medications unless they are specifically addressed, as patients may feel these products are not important, that they do not affect their other medications, or that the prescriber will disapprove of their use of these products (17,18).

A recent study utilized a community pharmacist-administered telephone survey to determine the use of over-the-counter (OTC) medications and supplements in patients with CKD (19). The survey found that 83% of patients with moderate CKD (creatinine clearance 30–60 ml/min) and 68% of patients with severe CKD (creatinine clearance $<$30 ml/min) were using one or more OTC medications. Contraindicated OTC and natural medications, such as aluminum hydroxide, ammonium chloride, and licorice were reported in 9% and 3% of patients with moderate and severe CKD, respectively. Patients also reported using OTC and natural medications for which caution should be used in CKD including ibuprofen, magnesium hydroxide, and salicylates. Patients reported that they had consulted a medical provider regarding only 49% of OTC medications, and 19% of natural supplements (19). Other commonly used supplements that may interfere with CKD medications include St. John's Wort, ginkgo and noni juice, among others (20). The frequent use of these products and their potential for interactions necessitates vigilant monitoring by healthcare providers and specific patient education to avoid medication-related problems.

Prescribing for patients with CKD also requires continual evaluation of each medication in the context of pharmacokinetic and pharmacodynamic changes associated with reduced kidney function. Pharmacokinetic changes related to CKD involve reduced oral absorption, changes in total body water and volume of distribution, changes in intestinal, hepatic and renal metabolism, alterations in tubular secretion and reabsorption, and reduced elimination through glomerular filtration (21,22). Similarly, pharmacodynamic changes involving physiological changes and alterations in receptor site affinity may influence drug sensitivity, thus contributing to adverse drug reactions (21). As renal function declines over time, serum concentrations of previously well-adjusted chronic medications may rise to unsafe levels due to accumulation. Conversely, some medications, such as thiazide diuretics, become less effective when kidney function is poor, necessitating a switch to an alternative agent (23). The onset of hemodialysis may cause some medications, such as vancomycin, to require increased dosage to maintain therapeutic concentrations in the face of dialysis clearance (24). Careful dosing adjustments based on the patient's creatinine clearance, dialysis clearance, and expert knowledge of drug pharmacology and interactions are required to manage alterations in pharmacokinetic and pharmacodynamic effects.

Medication-Related Problems in CKD

Overview

Providing optimal medication management involves assessment of each individual medication as well as critical review of the combined medication regimen to identify potential or actual medication-related problems. Most studies of medication-related problems in CKD have focused on dialysis (stage 5 CKD) patients (6,25–30). In these patients, the incidence of medication-related problems is higher in the presence of five or more medications, 12 or more medication doses per day, four or more changes in the medication regimen in the past 12 months, more than three concurrent disease states, history of nonadherence, drugs requiring therapeutic monitoring, and diabetes (6). In one study of 133 hemodialysis patients, at least one medication-related problem was identified in 97.7% of patients, with an average of four problems per patient (6).

A pooled analysis was conducted of seven studies involving pharmacist-conducted medication reviews of hemodialysis patients (12). In these studies, 395 ambulatory hemodialysis patients took an average of 11.8 medications to treat a mean of 6.2 concurrent conditions. Nearly 1600 medication-related problems were identified. Those occurring most frequently were inadequate laboratory monitoring (23.5% of all medication-related problems), subtherapeutic dosage or overdosage (20.4%), lack of treatment for an indication (16.9%), and medication treatment not warranted (14.9%). Failure to receive medication accounted for 4.8% of problems. Some studies included in the pooled analysis rated the significance of the interventions required to address the medication-related problems. Over 80% of interventions were rated as 4 (intervention improves level of care to acceptable standards) on a scale of 1–6, with 1 = intervention is detrimental to 6 = intervention is potentially life-saving (12).

Given the complexity of the concomitant medical conditions and number of medications encountered in patients on dialysis, the presence of this large number of medication-related problems is not surprising. Laboratory monitoring for medication efficacy and toxicity may fall to a low priority in the presence of other significant medical problems. Similarly, problems related to medication dosage are common, as changes are needed as renal function declines or dialysis is initiated. Untreated conditions may involve lack of evidence-based preventive therapy for diabetes, cardiovascular disease and other chronic conditions, thus putting the patient at increased risk of disease-related morbidity or mortality.

Nonadherence

Most medication-related problems are associated with suboptimal medication management. However, failure to receive therapy is a multifaceted issue involving medication accessibility and cost, as well as nonadherence related to other patient factors (31–33). A large international study conducted in 12 countries found that out-of-pocket medication spending by dialysis patients was highest in the U.S., averaging $114 per month in 2002–2004. Similarly, the proportion of patients reporting that they "sometimes decided not to purchase medications because of cost" was highest in the U.S. at 29% (31). In a survey of 54 chronic patients receiving hemodialysis or peritoneal dialysis, 30% chose not to fill a prescription because of either lack of funds or lack of transportation to the pharmacy (32).

Other factors also influence adherence. Dialysis patients are expected to maintain a complicated regimen that includes dietary and fluid restrictions, multiple medication dosages per day and attendance at prescribed dialysis sessions. It is estimated that about 50% of dialysis patients fail to adhere to at least part of their treatment regimen (34). This is consistent with the findings of the National Council on Patient Information and Education, who have labeled nonadherence as "America's other drug problem" (35). Although nonadherence is very widespread, it has been difficult to establish firm relationships between patient demographics and nonadherence in dialysis patients. The factors that have been identified as being associated with higher rates of nonadherence with the dialysis treatment regimen include younger age, African-American race, female gender, employed status, living alone, depression, and smoking. In addition, larger dialysis facility size is associated with lower adherence to the dialysis treatment schedule, perhaps indicating a relative lack of communication or personal attention to patients on the part of facility professional staff (33). A review of published papers regarding phosphate binder adherence revealed that psychosocial factors may be the best predictors of nonadherence, including patients' health beliefs, personality, and social support (36).

Although there is an abundance of literature identifying the problem of nonadherence, there is little consensus as to the best intervention to improve adherence. Adherence interventions for chronic diseases require a multifactorial approach that may include simplifying regimens, providing information and counseling, self-monitoring, reinforcement, and telephone follow-up (37). One study of 94 patients with diabetes and/or cardiovascular disease utilized an approach that included care managers that had received training on techniques for medication behavior change, motivational interviewing techniques and active listening (38). Patients in the study were identified by refill record reports indicating the patients were 60 days or more overdue on refills. Care managers discussed adherence aids and side effect management with patients during telephone follow-up. Patients receiving the care management demonstrated a higher rate of medication reinitiation and shorter time from medication nonadherence to adherence than patients in the control group (38). However, even with this targeted intervention, 38% of study patients remained nonadherent. Further studies are needed to define the best strategies for improving adherence.

Medication Record Discrepancies

Even when patients are taking their medications as prescribed, medication record discrepancies can pose a

risk for prescribing errors and their associated medication-related problems. Dialysis patients often move from one healthcare setting to another (e.g., hospital to dialysis unit, long-term care facility to dialysis unit) and there are often frequent changes in the medication regimen made by multiple prescribers, thus increasing the likelihood of inaccurate records.

A study evaluating the frequency of medication discrepancies compared patient medication use data obtained from pharmacist-conducted medication interviews to the clinic's electronic medical record list of medications (39). Over a 5-month period, 215 medication interviews were conducted in 63 patients. Of these, 38 patients (60%) had 113 medication record discrepancies, placing them at increased risk of adverse effects and dosing errors (39).

More recently, a study of 20 hemodialysis patients transferring from an in-center dialysis unit to a satellite unit found that nearly 80% had one or more medication variances, defined as a medication omission, an extra medication or a discrepancy in dose, frequency or dosage form (40). Of patients with a variance, an average of four discrepancies were found.

It is clear that medication reconciliation is needed, whenever a patient changes from one healthcare setting to another. In addition, due to the dynamic nature of dialysis patients' care and the number of healthcare providers involved, routine medication review is warranted to identify and resolve medication errors as well as optimize therapy.

Reducing the Risk of Medication-Related Problems: The Role of the Pharmacist

Structured medication reconciliation and assessment is the key to identifying, preventing, and managing medication-related problems. Several studies have utilized focused patient medication history interviews, medication profile reviews, and open communication between pharmacists and prescribers to identify and manage medication-related problems in patients with stage 5 CKD in hemodialysis units (6,25–30). In a pooled analysis of these studies, resolution of medication-related problems was found to improve the quality of patient care 89% of the time (12). One study reported that compared with usual care by the physician, ongoing pharmacist interactions with patients resulted in significantly better patient adherence, laboratory outcome parameters, and clinical status (25). Other settings in which structured medication assessment of CKD patients has been reported include community pharmacies, ambulatory care clinics, and managed care environments (41–44).

In the community setting, a study was conducted to assess the feasibility of a communication network between community pharmacists and providers in a predialysis clinic (41). Pharmacists with no specialized training in nephrology attended a 3-hour workshop reviewing basic drug therapy in CKD and identification of medication-related problems. They were also trained on the communication network used to provide recommendations to providers in the predialysis clinic. Over a 6-month period, 24 pharmacist recommendations included drug dosage adjustments, adding medications, and discontinuation of inappropriate or ineffective medications (25%, 21%, and 17% of recommendations, respectively) (41).

Two studies involved pharmacist management of high-risk indigent patient populations in ambulatory care clinics (42,43). Chart reviews of 119 patients were conducted by clinical pharmacists to identify patients with CKD and their medication-related problems in high-risk patients with hypertension and/or diabetes. Pharmacists made an average of 3.2 recommendations per patient. Recommendations included switching medications (9.2% of patients), altering dosage or dose interval (32.8% of patients), discontinuation of nonsteroidal anti-inflammatory drugs (26% of patients), adding a renoprotective or cardioprotective drug (ACE inhibitor/angiotensin receptor blocker in 18.5% of patients or low dose aspirin in 49% of patients), additional laboratory monitoring, meeting diabetes and blood pressure goals, and nephrologist referral (42). In a separate study, a pharmacist-based disease state management service for CKD risk reduction yielded improved compliance with national standards in a high-risk, indigent population (43).

Multidisciplinary CKD clinics have been recommended as a mechanism for caring for the complex and diverse needs of patients with predialysis CKD (45,46). Team members including physicians, nurses, dieticians, social workers, and pharmacists can each use their specialized clinical training and expertise to benefit these patients. As members of the team, pharmacists are uniquely qualified to provide undivided attention to medication assessment and management. For example, pharmacist-managed anemia clinics have been shown to improve attainment of clinical treatment goals as well as reduce the cost of therapy (47,48). Similarly, medication therapy management of other CKD-related conditions, such as hypertension, diabetes mellitus, hyperlipidemia, and bone and mineral metabolism disorders, as well as general medication therapy reviews can improve patient outcomes. A comprehensive review of the roles and demonstrated value of pharmacists in CKD patient care has been published elsewhere (49).

Medication management in CKD is not only able to improve clinical outcomes, but may have a large impact on reducing healthcare costs. In 2002, Manley and Carroll estimated the economic impact of clinical pharmacist involvement (eliminating unnecessary or inappropriate medication and preventing hospital visits) to be a potential $4 savings per dollar spent (50). Similarly, the impact of a CKD disease management program was assessed (44). This 6-month pilot study of 100 patients involved patient phone management by pharmacists and nurses trained in motivational interviewing and medication management. Authors reported an average of $300 per patient per month savings in combined prescription and medical costs for the managed group compared to the control group (44).

Structured Medication Optimization and Reconciliation Process

Although there are several studies describing the scope of the problem regarding polypharmacy in CKD, there is limited information regarding the actual process for identifying medication-related problems and reducing polypharmacy. After considering the previously identified types of medication-related problems and the reported assessment methods (6,7,27,51), the authors have devised a process for medication reconciliation and optimization to consider when assessing CKD patient therapy. Due to the progressive nature of CKD and the frequent therapy changes inherent in patients with complex medical problems, this assessment process should be revisited by the medical team upon any transfer of care from one environment to another and also on a routine basis during stable periods of dialysis care.

The steps include:

1. *Obtain an accurate medication list from the patient*. Ideally, a patient would bring his/her medications to the interview for inspection by the clinician. To obtain an accurate medication list, it is important to inquire about not only prescription medications, but questioning must also specifically address nonprescription medications and natural supplements as well as social drugs such as alcohol and tobacco, which can interact with other agents. A combination of open and closed-ended questions is often employed to give the patient an opportunity to recall all of his/her medications. Inquiries about supplement use delivered in a nonjudgmental way may help to ensure accurate reporting and strengthen the patient–provider relationship.
2. *Evaluate whether all medications are medically necessary (extra medication) or whether any medications need to be added (medication omission)*. Factors to consider include assessment of whether the patient's clinical status has changed, thus no longer requiring a particular medication. Also, medications that can worsen kidney function (e.g., nonsteroidal anti-inflammatory agents) may need to be removed from the regimen. In addition, medications may have been previously added to the regimen to treat the side effect of another medication. If either of these situations occurs, the provider can determine if a more desirable agent is available (without this side effect) or if the implicated medication is being used at the lowest effective dosage.

   In some cases review of the patient's medication list will reveal that additional medications or therapies are warranted. For example, if the patient is not meeting treatment guidelines and goals on the current regimen, providers can optimize treatment by adding an agent. Similarly, evidence-based preventive therapies for CKD progression or diabetes complications may be missing from the regimen.
3. *Assess whether current therapy represents the "drug of choice" for each indication, individualized for each patient*. Consider whether the current regimen is chosen to maximize benefit with the least risk of side effects. Also, are therapy goals being met with the current regimen? Costs of therapy must also be considered, including both those to the patient and to the health system. Care should be taken to select the most cost-effective agents, taking into account insurance coverage and patient out-of-pocket expenses. In cases where cost is of major concern to the patient, the best agent for that patient may not always be the one generally considered most effective. Even the most effective agents are of little use if the patient will not use the medication as prescribed.
4. *Evaluate the medication dosage and regimen*. Appropriate medication dosage is based on the patient's estimated creatinine clearance, concomitant disease states, and current clinical status. Issues to assess include the potential need for dosage adjustment for declining kidney function and simplification of the regimen by minimizing the number of dosage times/day, which may improve adherence.
5. *Screen for drug interactions and adverse effects*. A check for drug–drug interactions will further determine if a medication may be increasing the pharmacologic or toxic effects or blood concentration of another medication, necessitating a dosage decrease. Additionally, drug–disease interactions involving nephrotoxic medications or medications that should be used with caution in CKD patients (depending on renal function) can be identified and minimized. Inquiry regarding patient symptoms may help to identify potential adverse drug reactions. Since many patients may not associate an effect or symptom with a particular medication, providers may need to prompt patients regarding specific adverse effects potentially associated with their medications.

   One study of 214 men assessed three methods of inquiry regarding adverse effects (52). The researchers examined the number of adverse effects reported when using open-ended questions, open-ended defined questions, or a checklist of adverse effects commonly experienced. Men in the open-ended and open-ended defined question groups reported 11 and 14 adverse effects, respectively. In contrast, the men in the checklist group reported 238 adverse effects (52). Providers asking about specific adverse effects may obtain more information from patients. When adverse reactions are identified, providers may remove the offending agent or offer suggestions to manage the effect.
6. *Assess the monitoring plan*. Once a regimen is determined, providers can determine if additional laboratory monitoring is indicated to

determine the patient's current renal function, to monitor medication efficacy or toxicity or to measure other relevant clinical indicators. Concomitant disease states should be evaluated along with screening for comorbidities associated with CKD.

7 *Determine whether there are any barriers to patient adherence*. After an appropriate medication regimen is established, patient-perceived barriers to adherence can be identified and addressed. This step in the process may lead providers to reevaluate the patient's regimen or provide additional patient education to facilitate adherence. Identification of medication adherence is typically achieved through patient self-reports and clinical interviews. A recently developed clinical interview approach encourages clinicians to inquire about adherence over a specified time frame (e.g., How many times have you missed this medication in the last 7 days?) (53). These types of interview questions prompt the patient to be more specific and may help providers identify issues with specific medications or administration schedules. Patient knowledge gaps regarding appropriate administration of medications can also be identified (such as whether the patient is taking phosphate binders with meals) and addressed accordingly.

8 *Identify and resolve any discrepancies between the medication list obtained from the patient and the medical record*. The final step in the process is to compare the medication list that was developed through the review process to the list in the medical record. Any discrepancies should be resolved and documented.

Conclusion

Medication-related problems are common in CKD patients and necessitate a comprehensive approach to their identification, prevention and management. The comorbid conditions and complex regimens necessary to manage CKD patients make medication-related problems almost inevitable. Detailed patient interviews and structured medication assessments may facilitate the identification and prevention of these problems. Once the potential or actual drug-related problems are identified, a collaborative effort involving open communication between healthcare providers and patients can be made to resolve these therapy issues. Regular assessment and management of medication-related problems in CKD patients is one step providers can take toward optimizing CKD medication therapy and attempting to slow progression of the disease.

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