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Editorial Comment

EDITORIAL COMMENT

Is polypharmacy an increasing burden in chronic kidney disease? The German experience

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ABSTRACT

This is a commentary article describing the key findings of the German chronic kidney disease (GCKD) study and how these relate to current practice. With the GCKD study showing high levels of polypharmacy, this article discusses ways to ensure that polypharmacy is appropriate and the difficulties faced within a chronic kidney disease population. Suggestions of ways to minimize medication burden in renal patients provide some practical advice for clinicians.

Keywords: chronic kidney disease, deprescribing, medication burden, polypharmacy, prescribing patterns

BACKGROUND

Polypharmacy is becoming an increasing problem due to the increasing elderly population with multiple comorbidities [1–3]. Very few studies have looked at this burden in chronic kidney disease (CKD) populations [4–6], thus the German CKD (GCKD) study investigators report their findings from a large cohort of CKD patients [7]. This study provides us with a better understanding of polypharmacy and prescribing practices in CKD patients and highlights the need for us as clinicians to consider this burden at each patient contact and when making prescribing decisions.

WHY IS POLYPHARMACY RELEVANT?

When treating patients with many comorbidities, the use of multiple medications may be indicated and be of benefit. However, the use of numerous medications poses safety risk to patients [8]. The presence of polypharmacy has been linked with a range of unfavourable effects, including drug–drug interactions, medication non-adherence, inappropriate prescribing, adverse drug events, hospitalization, falls, functional decline and mortality [8].

Conversely, some studies find no correlation between polypharmacy and increased hospital admissions [9], suggesting polypharmacy can be appropriate. The definition of appropriate polypharmacy is the 'optimisation of medications for patients with complex and/or multiple conditions where medication use agrees with best evidence' [10]. The GCKD study group certainly suggests that there are some elements of appropriate polypharmacy within their work, with those on blood pressure–lowering medications having improved blood pressure readings versus those who were not on treatment [7].

Inappropriate polypharmacy not only encompasses overprescribing and incorrect prescribing, but also underprescribing. This is a particularly well-recognized issue in the older population [11]; paradoxically, some medications are not prescribed, due to fear of adverse drug events, leading to adverse outcomes [12].

Achieving a fine balance between appropriate and inappropriate polypharmacy is key for patients, and in CKD this may be more difficult when faced with a lack of evidence.

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WHAT ARE THE ISSUES WITH POLYPHARMACY AND CKD?

The burden of medication in the GCKD study is high, with some patients taking nearly 30 different medications a day [7], which seems unreasonable for patients to manage. In the study, 20% of patients took >10 different medications per day [7]. Increasing CKD stage was associated with an increased number of medications, which is similar to the findings in the Chronic Kidney Disease–Renal Epidemiology and Information Network (CKD-REIN) study [6, 7]. It is unclear whether the additional complications associated with CKD progression are responsible for the increase in medication or if new therapies have just been added to the original medication regimen in the GCKD study. The recently published CKD-REIN study included a large number of CKD patients in France with an estimated glomerular filtration rate <60 mL/min/1.73 m^2 and found that a high proportion of medications were contraindicated for current renal function, suggesting a lack of prompt review as renal function deteriorated. The main contraindicated drugs reported were metformin and non-steroidal anti-inflammatory drugs (NSAIDs) [6]. The GCKD study showed a number of patients had been prescribed NSAIDs, with 6.6% of patients being on them at the start of the study and 5% remaining on NSAIDs at follow-up [6]. Whether these same patients remained on NSAIDs is unknown, but it raises concerns about how appropriate these prescriptions were. Long-term NSAID use may not always be appropriate in CKD patients, especially given the high number of patients in the study taking antihypertensives. NSAID use may also be contributing to the high prescription rates of proton pump inhibitors that the study reported, potentially due to co-prescription.

Medication burden to this extent is likely to have an impact on medication adherence, and we are already aware that non-adherence is a big problem. Data suggests that 50–80% of patients do not take their medications as prescribed [13], and this has been shown in patients with severe CKD [14–16]. The palatability of certain medications used in CKD, such as phosphate binders, are another issue, not only creating a high burden in themselves [4], but also being notably distasteful and requiring strict timing regimens [17, 18]. Hard data on patient outcomes with phosphate binders are lacking [19] and observational studies are what guide the current recommendations, with a lack of clarity on exactly what phosphate levels should be targeted [20]. This can make it more difficult to explain to patients why they should take these treatments, especially with recent bad press, which can have quite an influence on patient's views [21]. Reports of adherence to phosphate binders have been as low as 22% [17]. Another class of medicines widely prescribed in the GCKD study (nearly 50% of patients) was the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. The authors suggest that an additional 40% of eligible patients were not taking HMG-CoA reductase inhibitors as per guideline recommendations. Studies following the negative media relating to side effects of this class of medication suggest that patients were more likely to cease or not commence new prescriptions of HMG-CoA reductase inhibitors when indicated [22, 23].

Patients should be encouraged to be involved in their treatment decisions in a collaborative process of shared decision making with health professionals [24, 25]. This shared approach to decision making facilitates patient understanding and medication taking [26], optimizing medication use for the best possible outcomes [27]. However, this process requires clear, evidence-based information about possible treatment outcomes, which may not be available for certain medications in more advanced CKD. Areas of ongoing debate are the use of anticoagulants for atrial fibrillation in the dialysis population [28, 29] and the use of native vitamin D (cholecalciferol) in those with severe CKD [30, 31]. Good-quality research studies are not available to guide practice in such populations and the individual clinician's opinion may be the overriding factor affecting therapy initiation. Ensuring that prescribing is evidence based is one of the key challenges to achieving appropriate polypharmacy, as CKD patients are underrepresented in clinical trials.

Another key point highlighted by the GCKD study is the contribution of over-the-counter (OTC) and complementary medicines to polypharmacy in CKD patients. This is something that is poorly discussed at patient consultations due to time constraints, but it could have a significant impact on medication burden, drug interactions and adverse effects. A large number of patients were taking vitamin supplements, nearly 1900 at the start of the study, as people perceive these as beneficial. However, as renal function declines they may be more harmful than beneficial. A number of other patients were taking other supplements and complementary medicines. Complementary medicines have extremely limited data in general for both safety and efficacy, and pharmacokinetics or interactions are seldom studied. With this limited information, it makes it extremely difficult to provide advice in such a complex population with high numbers of medications, medical conditions and altered pharmacokinetic handling of drugs. One example of non-prescribed products that have been the subject of great discussion by kidney patients in recent months is products containing cannabidiol (CBD) [32]. There are lots of poor-quality Internet resources suggesting that CBD oil may help kidney disease. This is sold as a health food supplement in the UK and thus does not fall under the Human Medicines Regulations 2012, resulting in the presence of small amounts of tetrahydrocannabinol (THC) in some products [33]. THC can certainly lead to numerous adverse effects in kidney patients, and both CBD and THC are renally excreted, leading to potentially prolonged effects [34]. The other concern with these products includes interactions with drugs metabolized by CYP3A4 [35], such as tolvaptan and tacrolimus/ciclosporin, which could certainly lead to problems in CKD patients.

Addressing such a high medication burden is not easy when trying to ensure that the polypharmacy is appropriate, but involving the renal multidisciplinary team (MDT) will be extremely beneficial to support busy clinicians and benefit patients [36, 37]. There is some evidence that clinical pharmacist involvement in CKD patient care led to increased medication knowledge [38], decreased hospitalization rates [39] and produced an overall improvement in the quality of life in dialysis patients [40].

WHAT CAN WE DO?

A systematic review that looked at factors affecting patient medication-related burden highlighted a number of issues, including managing medication routines; medication characteristics, such as the size of tablets and frequency of administration; adverse effects and the associated social burden [41]. A number of these issues can be easily addressed in a CKD population, as outlined in Table 1.

Medication regimens can become more complex with increasing polypharmacy, which may lead to non-adherence. Identifying the reasons for non-adherence is key to enable implementation of solutions to tackle this and improve patient outcomes. Non-intentional non-adherence due to difficulty remembering complex regimens may be overcome by supporting

Table 1. Polypharmacy-related problems and ways we can manage these in CKD patients

Polypharmacy-related problem	Method of ensuring polypharmacy is appropriate and manageable
Burden of medication regimen	Optimize current medications before adding additional therapies; stop ineffective medications; compliance aids
Complex medication characteristics	Use drugs that have a lower frequency of administration, modified release preparations if available or combination tablets if available; if possible, avoid drugs with complex administration instructions, e.g. timing with/without food; involve the patient in incorporating the medication regimen into his/her lifestyle; assess tablet size/palatability with patients
Lack of evidence	Involve patients in discussions regarding therapies that are lacking good evidence
Adverse effects	Highlight to patients the adverse effects of new medicines to allow early detection; assess at each clinical contact
Over-the-counter/homeopathic	At each contact, ask about the use of these agents; refer to a pharmacist for further advice if required; highlight to the patient that he/she should discuss non-prescribed treatments with the clinician prior to taking

patients with adjusting medications around lifestyle factors or introducing compliance aids where appropriate. The frequency of medication administration also plays a role in patient burden and opting for a once daily antihypertensive versus one that is taken three or four times daily would be preferable in reducing tablet burden.

The role of deprescribing by rationalizing medications, ensuring patients are on the most effective combination of medication and stopping ineffective medications, can simplify medication regimens [42]. One example would be optimizing the dose of an antihypertensive before adding an additional agent. There is a validated tool for medication complexity that helps to consider the medication-dosing regimen, but this can be time consuming to assess, especially in an outpatient clinic setting [43]. Another tool with a basic set of prompts can help assess for medication appropriateness when initiating a new therapy [44].

Medication characteristics can be problematic for patients, such as the size and palatability of phosphate binders. Offering alternative options to patients who are struggling may improve adherence.

Ensuring that prescribing is evidence based is one of the key challenges to achieving appropriate polypharmacy. Providing patients with relevant information and involving them in decisions means that they are more likely to accept of the therapy.

The complications associated with declining renal function are relatively non-specific and may mask adverse effects related to medications. We need to remain vigilant to recognize adverse effects, especially given that a misdiagnosis as a complication of CKD may lead to additional prescribing—the process known as the prescribing cascade. Counselling patients on common adverse effects to newly prescribed medications may assist in early detection.

Over-the-counter medicines and vitamin supplements are something, as clinicians, that we do not always consider or have time to ask about. The GCKD study shows high usage of these agents, which is quite concerning, and we should ensure that this is discussed at each patient contact. Concerns about using these agents should be highlighted to ensure that patients discuss them with their health professional prior to taking.

CONCLUSION

The GCKD study adds significantly to the literature that CKD patients are exposed to substantial polypharmacy, and some of this may well be appropriate. To ensure we are managing our CKD patients with the best pharmacological options, an MDT approach may be warranted. By supporting patients to reduce the burden that medication has on their lives, including ensuring appropriate polypharmacy, involving them in medication-related decisions and highlighting potential risks of over-the-counter/herbal medications, may improve adherence, safety and outcomes. The GCKD study has provided data on polypharmacy, but further studies are still required to show the impact this has on CKD patients and adherence and how appropriate it is in a CKD population.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole, in part or in abstract form.

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