Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

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Inappropriate prescribing in renal impairment: its prevalence, consequences and the impact of interventions to improve prescribing

A systematic review has evaluated the prevalence of inappropriate prescribing (IP) in patients with chronic kidney disease (CKD) and its association with adverse clinical outcomes. There was an association between IP and increased length of hospital stay, mortality, adverse drug reactions and higher expenditure in patients with CKD. Predictors of IP include older age, late-stage kidney disease, high number of medications (polypharmacy) and the presence of multiple co-morbidities. Pharmacist-based interventions improved clinical outcomes more than computer-based interventions.

Reference: Tesfaye WH, Castelino RL, Wimmer BC *et al.* Inappropriate prescribing in chronic kidney disease: a systematic review of prevalence, associated clinical outcomes and impact of interventions. Int J Clin Pract. 2017 May 23. doi: 10.1111/ijcp.12960. [Epub ahead of print]

What do we know already?

- Renal impairment may alter drug pharmacokinetics (potentially affecting efficacy and the likelihood of adverse effects) and induce pharmacodynamic changes e.g. uraemia which may alter the clinical response to drugs. Clinical consequences may include increased sensitivity to drugs acting on the central nervous system; and increased risk of gastrointestinal bleeding with non-steroidal anti-inflammatory drugs.
- Drugs and/or metabolites that depend on the kidney for excretion may accumulate in people with renal impairment. This generally becomes a clinical concern when at least 30% of the drug and/or active metabolite(s) are eliminated via the urine, and for these drugs, dosage adjustment is necessary.[1]
- Single doses of a drug given to patients with renal impairment are not usually considered to be dangerous as accumulation is unlikely. However, with repeated dosing, three strategies may be employed to help optimise therapy and avoid unnecessary adverse effects[2]:
    - Administering standard doses at extended intervals (usually used for drugs for which specific peak serum concentrations need to be achieved).
    - Reduced doses at the usual dosing interval (usually used with drugs that require maintenance of a serum concentration over the dosing interval).
    - A combination of reduced doses and extended interval.
- A UKMI publication from 2016 provides a useful review of the factors requiring consideration when dosing patients with renal impairment.

What does this evidence add?

- This study is the first comprehensive systematic review to summarise the prevalence of IP in patients with CKD and assess the impact of interventions to reduce IP. It is also the first review to assess clinical outcomes associated with IP and the factors contributing to it.
- The study confirms an association between IP and increased length of hospital stay, mortality, adverse drug reactions and higher expenditure in patients with CKD. Predictors of IP include older age, late-stage kidney disease, high number of medications (polypharmacy) and the presence of multiple co-morbidities.
- Clinical outcomes showed better improvement following pharmacist-based interventions rather than computerised interventions, highlighting the value of the human-based intervention and the positive role of the clinical pharmacist in identifying, advising and optimising medication for patients with CKD.

Study details

- The authors screened 10,183 citations published between 1992 and 2015 and included 49 studies in the review from 23 countries, predominantly the USA (n = 11) and Australia (n = 5). Studies were included based on the following inclusion criteria: CKD was clearly defined, IP was evaluated objectively and the prevalence of IP was quantified or could be extracted from the data.
- 43 studies were rated as moderate or high quality and nine of the included studies had more than 1,000 study participants.
- CKD was defined as a reduction in glomerular filtration rate (GFR) and/or kidney damage (haemattururia or proteinuria) lasting at least 3 months. IP was defined as prescribing medication at an incorrect dose/frequency and/or prescribing medication contraindicated based on the patient's renal function.
- Most studies used Cockcroft Gault (CG) to estimate renal function for drug dosing (n = 26) while 16 studies used the modification of diet in renal disease (MDRD) equation. Six studies employed either Jelliffe's equation or a combination of formulas to determine renal function status (note that the interchangeable use of these equations in patients could have resulted in varied dose recommendations and subsequent disparity in IP reporting).

Results:

- The prevalence of IP varied from 9% to 81.11% and 13% to 80.5% in hospital and ambulatory settings, respectively. Similarly, the IP prevalence in non-institutionalised community-dwelling patients ranged between 25.9% and 52.6% (and 96% in those with an eGFR<30ml/min/1.73m^2), and between 16% and 37.9% in those in long-term care facilities.
- 21 studies reported on the impact of interventions on IP. Immediate concurrent feedback to physicians was found to provide the highest reduction in IP (from 77% to 19%, $p < 0.001$). Conversely, simple eGFR reporting to physicians in ambulatory and hospital settings did not significantly reduce IP (64% to 68% and 44% to 40%, p = 0.9 and p = 0.81 respectively).
- Seven studies measured the extent to which physicians accepted pharmacists' recommendations, which ranged from 31.4% to 95.7%.
- Nine studies reported perceived barriers to appropriate prescribing including poor awareness of physicians to guidelines, reluctance to alter dose, relying on trend-based clinical practice, lack of laboratory and clinical information to make a decision, alert fatigue from computerised-decision support systems and the wide therapeutic range of some medication.
- Commonly reported classes of medication prescribed inappropriately included antidiabetics, histamine-2 antagonists, antibiotics, and cardiovascular drugs (mainly angiotensin-converting enzyme inhibitors). Metformin was the most inappropriately prescribed medication (41.5% to 84.6% of prescriptions).
- Older age, late-stage kidney disease, high number of medications (polypharmacy) and the presence of multiple co-morbidities were significantly associated with IP. While age, the number of medications and co-morbidities were associated with IP in community-dwelling patients, stage of CKD and number of medication were factors in hospital settings.
- Eight studies reported clinical outcomes showing an association between IP and increased length of hospital stay, mortality, adverse drug reactions and higher expenditure – many of which are potentially preventable with simple dose-checking and adjustment. Of note, clinical outcomes showed better improvement following pharmacist-based interventions when compared with computerised interventions, showing the value of the human-based intervention and the positive role of the clinical pharmacist.

Level of evidence:
Level 2 (limited quality patient-oriented evidence) according to the SORT criteria.

Study funding:
No source of funding is reported.