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DOI:
10.1007/s40264-021-01099-3

Document Version
Peer reviewed version

Citation for published version (Harvard):
Alruqayb, WS, Price, MJ, Paudyal, V & Cox, AR 2021, 'Drug-related problems in hospitalised patients with chronic kidney disease: a systematic review', *Drug Safety*, vol. 44, no. 10, pp. 1041–1058. https://doi.org/10.1007/s40264-021-01099-3

Drug-Related Problems in Hospitalised Patients with Chronic Kidney Disease: A Systematic Review

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Abstract

Introduction:

Globally, Chronic Kidney Disease (CKD) is one of the leading causes of mortality. Impaired renal function makes CKD patients vulnerable to drug-related problems (DRPs).

Aim

The aim of this systematic review was to investigate the prevalence and nature of DRPs among hospital in-patients with CKD.

Methods

A systematic review of the literature was conducted using Medline, EMBASE, PsycINFO, Web of Science (Core Collection), CINAHL plus (EBSCO), Cochrane Library (Wiley), Scopus (ELSEVIER) and PubMed (U.S.NLM) from index inception to January 2020. Studies investigating DRPs in hospitalised CKD patients published in English language were included. Two independent reviewers extracted the data and undertook quality assessment using Joanna Briggs Institute (JBI) tool.

Results

A total of 2895 unique titles were identified; with 20 meeting the inclusion criteria. DRPs prevalence in CKD was reported between 12% to 87%. The most common DRPs included ineffective treatment, inappropriate drug choice, and dosing problems. Antibiotics, H2-antihistamine and oral antidiabetics (metformin) were common drug classes involved in DRPs. Factors associated with DRPs included severity of CKD, the number of medications taken, age, length of hospital stay, and gender.

Conclusion

This systematic review provides evidence that DRPs are a frequent occurrence and burden for hospitalised patients with stage 1-4 CKD. Heterogeneity in study design, case detection and definitions are common, and future studies should have use clearer definitions and study designs.

Protocol Registration: PROSPERO: CRD42018096364

Key points:

- Drug related problems occur frequently and are a burden for hospitalised patients with stage 1-4 chronic kidney disease.
- Antibiotics are the common causes of these drug related problems and the severity of chronic kidney disease is associated with Drug related problems.
- Uniform guidelines for chronic kidney disease patients including estimating renal function, and drug and dose recommendations, might reduce drug related problems.

Declarations:

Funding Sources

The study was funded by the University of Birmingham, and The Saudi Cultural Bureau funded Wadia Alruqayb's PhD studies. MJP is supported by the NIHR Birmingham Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Conflicts of interest/Competing interests

Wadia S Alruqayb, Malcolm J Price, Vibhu Paudyal and Anthony R Cox have no conflicts of interest relevant to the content of this study

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material:

Collated data from the study is available from the authors on request.

Code availability:

Not applicable.

Authors' contributions:

All authors contributed to this systematic review and writing the manuscript. WA conducted the searches, data extraction and synthesis, with contributions and review by VP and AC. MP reviewed the data and synthesis.

All authors read and approved the final version of the manuscript.

1. Introduction

Chronic Kidney Disease (CKD) is defined as “abnormalities of kidney structure or function, present for 3 months, with implications for health”, and classified based on cause, glomerular filtration rate (GFR) category, and albuminuria category (CGA) (Levin et al., 2013). This results in the inability of the kidneys to filter the blood resulting in excessive build-up of fluid and waste products (e.g. drug or its metabolites). Additionally, the pharmacokinetics and pharmacodynamics of several medicines is altered due to the physiological changes in the kidney (Berns). Alterations in the absorption, distribution, metabolism and excretion of drugs may require dose adjustments (Cao, 2020). Some medicines may cause an additional decrease of kidney function or lead to further kidney dysfunction through different mechanisms. For example, cyclosporine can alter the intraglomerular haemodynamics of the kidney (Pannu and Nadim, 2008).

Approximately 1.2 million deaths occurred associated with CKD in 2015 globally, with estimates of 40,000 to 45,000 deaths every year in the UK (Kerr et al., 2012, Wang et al., 2016). A 2016 meta-analysis of observational studies on CKD global prevalence, based on 100 studies, found that the estimated global prevalence of all CKD stages was 13.4% (Hill et al., 2016). According to Public Health England, in the UK, 2.6 million people aged ≥16 years have CKD stage 3-5, representing 6.1% of this population group (Public Health England, 2014). This is expected to rise to 7.5% and 9.6% in 2021 and 2036, respectively (Public Health England, 2014). CKD care cost the NHS £1.45 billion between 2009 and 2010 (Kerr et al., 2012).

Medication is used to prevent, treat or diagnose illnesses. Yet, when medicines are prescribed, drug-related problems (DRPs) can reduce quality of life and lead to associated morbidity and mortality. Many DRPs are preventable depending on

detection of the source of the problem and causative factors (Adusumilli and Adepu, 2014, Hepler and Strand, 1990). A DRP is defined as “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes” (Van Mil et al., 2020). DRPs include three subcategories: adverse drug event/effect (ADE), adverse drug reaction (ADR) and medication error (ME) (Leendertse et al., 2008). ADE is defined as “an adverse outcome that can be attributed, with some degree of probability, to an action of a drug” (Aronson and Ferner, 2005). ADR is defined as “an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product” (Aronson and Ferner, 2005). Medication errors are defined as “a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient” (Ferner and Aronson, 2006). Such DRPs contribute to a remarkable burden of mortality, morbidity and healthcare spending all over the world (Ruths et al., 2007, Wester et al., 2008, Rozich and Resar, 2001).

Patients with CKD are at a high risk for DRPs because of an increased incidence of co-morbidities, and associated use of multiple medications (Quintana-Bárcena et al., 2018, Adibe et al., 2017). An observational study of 100 CKD patients, conducted in a large hospital in Turkey, found 80% of the participants experienced a DRP (Abunahlah et al., 2018). Another study concluded that inappropriate medicine use was 40% more likely in CKD patients compared with non-CKD patients (Breton et al., 2011).

A 2018 Malaysian hospital study found that 17.5% of hospitalised CKD participants died after an ADR, with the degree of renal impairment significantly associated with mortality after ADR (Danial et al., 2019). Previous reviews have focused on

hospitalisation due to medication problems in the general population (Nivya et al., 2015, Patel et al., 2017), with one review specifically focused on medication problems in non-hospital renal patients (Dorks et al., 2017). While a systematic review focusing only on inappropriate prescribing in chronic kidney disease in different settings, either community or hospital, exists (Tesfaye et al., 2017), to date, no systematic review has been conducted on the prevalence and risk factors contributing to DRPs in hospitalised patients with CKD. Therefore, a systematic review was carried out to provide a current assessment of the epidemiology of DRPs in hospitalised patients with CKD. This can be described using the cocopop mnemonic (condition, context, and population) as the prevalence of DRPs, and its subcategories, in adults (≥ 18 years) hospitalised with chronic kidney disease (Stages 1–4) (Stages 1-4) (Munn et al., 2015).

2. Methods

This systematic review was conducted based on Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols 2015 (PRISMA-P) (Moher et al., 2015) and is registered in the International Prospective Register of Systematic reviews (PROSPERO): (CRD42018096364) (Alruqayb et al.).

2.1 Literature search

Eight databases, including MEDLINE, EMBASE, PsycINFO, Web of Science (Core Collection), CINAHL plus (EBSCO), Cochrane Library (Wiley), Scopus (ELSEVIER) and PubMed (NCBI). The literature search was carried out using natural language keywords and, where applicable, MeSH terms. Each database was searched using variants of keywords such as drug-related problem (DRP), adverse drug reaction (ADR), adverse drug event (ADE), medication error (ME), hospitalised patients and chronic kidney disease (CKD). In all databases, the search was conducted from index

inception to January 2020 when the search was conducted. The reference lists of included studies and potentially relevant systematic reviews were reviewed to search for any additional studies (search strategy in appendix-1). This step was conducted independently by two reviewers (WA and AC) and reviewed by the third reviewer (VP).

2.3 Types of Studies and Eligibility Criteria

Studies on DRPs or subcategories in adult (≥ 18 years) hospitalised patients of both genders that included data on CKD stage 1–4 (GFR > 15 mL/min/1.73 m2) were included. This review excluded stage 5 as patients in CKD stage 5 are considered a special group since they require dialysis, which may be a confounder in detecting DRPs. However, the search was not restricted to studies that report all stages of CKD or those that reported only some. For example, if a study reported CKD stage 3 and 4 only, it was included. If stage 5 was included we read the study and extracted data on other stages if possible (in which case it was included), but if this data could not be extracted the study was excluded. We used the KDIGO classification (Levin et al., 2013), which considers stage 1 and 2 as CKD, but in the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfil the criteria for CKD. However, although they have minor effects on drug handling, we decided to include them.

Cross-sectional studies, cohort studies, case-control studies and interventional studies that report demographic data and prevalence of DRPs in hospitalised patients with CKD (at baseline for the intervention group or for the control group) were included. Search was not restricted by country, although an English language restriction was applied.

Dialysis patients were excluded as they are dependent on renal replacement therapy (RRT). Studies investigating DRPs as a reason for admission/readmission were excluded. Furthermore, abstract-only publications and grey literature were excluded.

2.4 Study Selection and Data Extraction

The articles found in the database search were transferred to Rayyan, a web application for systematic reviews, to identify and delete any duplicated articles (Ouzzani et al., 2016). Two reviewers (WA and AC) performed the screening and selection procedure. Firstly, titles and abstracts for each study were screened. The full text was reviewed based on the systematic review inclusion and exclusion criteria (if the full text is not available, the corresponding author and/or journal was contacted). Disagreements were resolved through discussion with the third reviewer (VP). A PRISMA flow diagram was used to illustrate all stages of the selection process (Moher et al., 2015). At the full text screening stage, reasons for exclusion were recorded.

Data extraction was performed using a bespoke form developed for the study and was piloted on sample papers prior to its use (appendix-1). Data on participant demographic characteristics; study design, setting and duration; the prevalence of CKD; the study population; author, year of publication and country of study origin; methods of estimating kidney disease; characteristics of DRPs (prevalence, types and most common drug classes); causes of DRPs; DRP risk factors and DRP classification system used were extracted. WA and AC extracted the data and VP reviewed and solved any disagreements.

2.5 Quality assessment

Two reviewers (WA and AC) independently critically appraised the included studies for the systematic review, any disagreement solved by discussion, using the Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data tool (Munn et al., 2014). This previously validated tool uses four simple answers, ‘Yes’, ‘No’, ‘Unclear’ and ‘Not applicable’ (appendix-1).

2.6 Meta-Analysis

Due to the clinical and methodological heterogeneity of the studies found, meta-analysis was not possible. Heterogeneity was found in measures and definitions of the presentation of results (such as the denominator and numerator). There was also heterogeneity in the description of participants (adult, elderly) and demographic data.

3. Results

3.1 Search Result and Study selection

A total of 2895 unique titles were identified from the eight databases. Of these, 121 were reviewed in full text, and 19 were included. One more study was included from searching the reference lists of the included studies, resulting in 20 studies in total (Figure1).

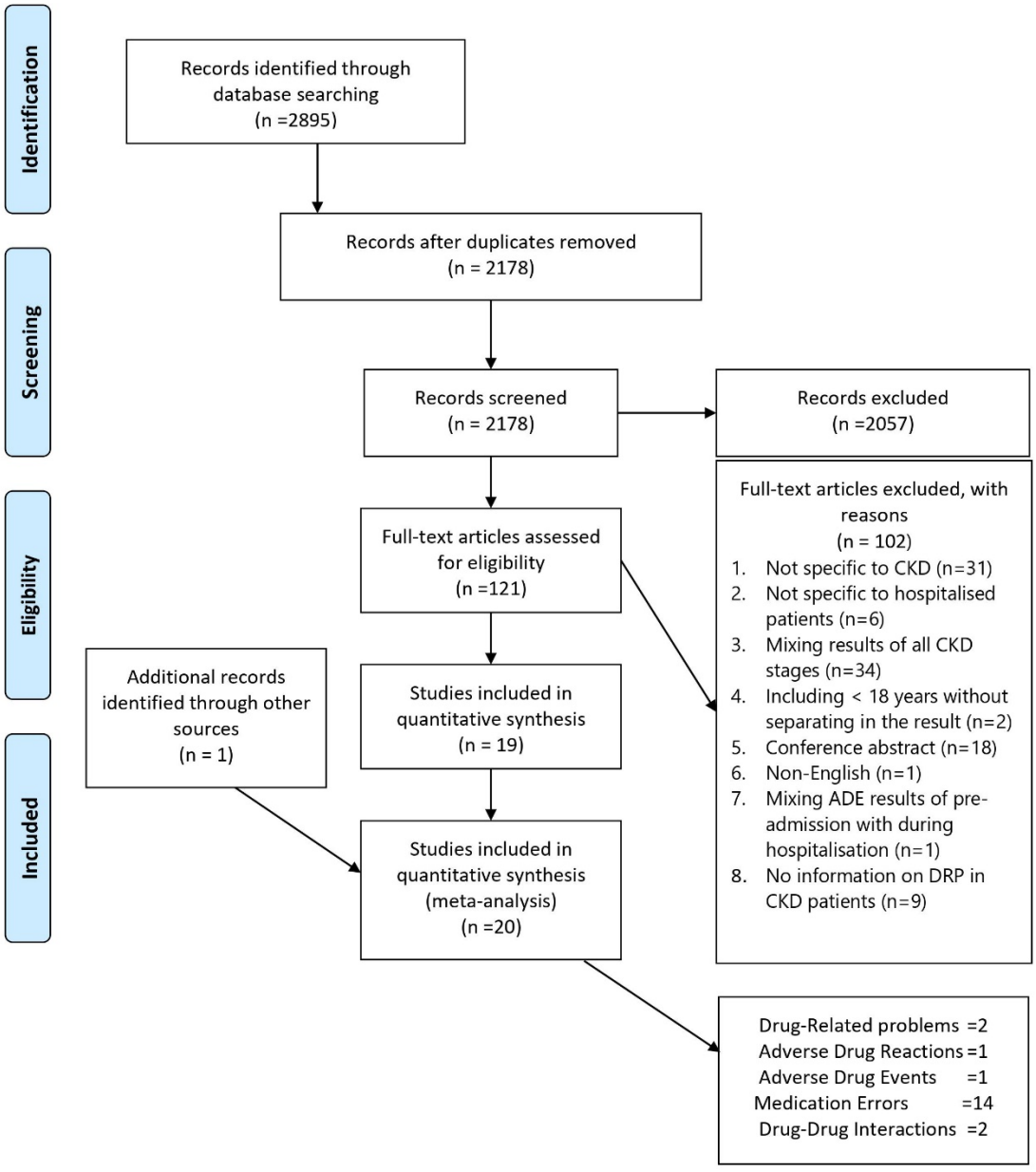

Figure 1: PRISMA Flow Diagram of Retrieved Studies. ADE adverse drug event, CKD chronic kidney disease, DRP drug-related problems.

3.2 Quality Assessment

The 20 studies were generally of good quality, however, only five studies had an adequate sample size to provide a reliable prevalence estimate (Sheen et al., 2007, Gomez-Lobon et al., 2012, Shigematsu et al., 2017, Won et al., 2018, Garedow et al., 2019). Inappropriate sampling frame was apparent in eight studies (Sweileh et al., 2007, Prajapati and Ganguly, 2013, Manjula Devi et al., 2014, Juarez-Cedillo et al., 2016, O'Shaughnessy et al., 2017, Getachew et al., 2015, Yang et al., 2016, Won et al., 2018). Further analysis was needed in eight studies (Sheen et al., 2007, Markota et al., 2009, Gomez-Lobon et al., 2012, Shalini et al., 2013, Nielsen et al., 2013, Manjula Devi et al., 2014, Juarez-Cedillo et al., 2016, Yang et al., 2016) (appendix-1).

3.3 Description of included studies

3.3.1 Settings and Countries

The majority of studies (60%) were conducted in Asia (Manjula Devi et al., 2014, Prajapati and Ganguly, 2013, Saleem and Masood, 2016, Saleem et al., 2017, Shalini et al., 2013, Sharif-Askari et al., 2014, Sheen et al., 2007, Sweileh et al., 2007, Shigematsu et al., 2017, Taner et al., 2018, Yang et al., 2016, Won et al., 2018), followed by Europe (25%) (Holm et al., 2015, Markota et al., 2009, Nielsen et al., 2013, O'Shaughnessy et al., 2017, Gomez-Lobon et al., 2012), Africa (10%) (Getachew et al., 2015, Garedow et al., 2019) and one in North America (5%) (Juarez-Cedillo et al., 2016). Most (n = 17) of the studies were carried out in different hospital departments while three were conducted in nephrology units only (Saleem and Masood, 2016, Saleem et al., 2017, Sharif-Askari et al., 2014) (Table.1). All studies were single-site studies, apart from one that was a secondary analysis of a multicentre study (Shigematsu et al., 2017).

3.3.2 Study design

The majority of the studies were retrospective (55%), with a variety of observational methodological designs (Table 1). Two studies included patients after checking their serum creatinine (SCr) for the previous 3 months or diagnosis of CKD reported in patients' notes (Juarez-Cedillo et al., 2016, O'Shaughnessy et al., 2017). For all others, a patient's eligibility was assessed by inspecting either one reading of SCr or the most current SCr (Table.1).

3.3.3 Study population

A total of 29,702 participants were included across the 20 studies, although nearly 90% of these were involved in a 4-year retrospective digital medical record review study at a tertiary teaching hospital (Table.1) (Sheen et al., 2007). Two studies only included geriatric patients (aged ≥70 years) (Juarez-Cedillo et al., 2016, Won et al., 2018).

3.3.4 Method of Estimating Kidney Function

Modification of Diet in Renal Disease (MDRD) was used in eight studies (Holm et al., 2015, Markota et al., 2009, Nielsen et al., 2013, Saleem and Masood, 2016, Shalini et al., 2013, Sharif-Askari et al., 2014, Sheen et al., 2007, Shigematsu et al., 2017); seven studies used Cockcroft-Gault (CG) CG (Getachew et al., 2015, Juarez-Cedillo et al., 2016, Prajapati and Ganguly, 2013, Sweileh et al., 2007, Taner et al., 2018, Yang et al., 2016, Won et al., 2018); A combination of MDRD and CG was used in three studies (Manjula Devi et al., 2014, O'Shaughnessy et al., 2017, Gomez-Lobon et al., 2012); while two studies did not report the method (Garedow et al., 2019, Saleem et al., 2017), (Table.1)

3.3.5 CKD classification

Six studies included all CKD stages (Juarez-Cedillo et al., 2016, Manjula Devi et al., 2014, Saleem et al., 2017, Sheen et al., 2007, Taner et al., 2018, Garedow et al., 2019); while nine studies were conducted on stage 3-5 (Getachew et al., 2015, Markota et al., 2009, O'Shaughnessy et al., 2017, Prajapati and Ganguly, 2013, Saleem and Masood, 2016, Sharif-Askari et al., 2014, Sweileh et al., 2007, Gomez-Lobon et al., 2012, Won et al., 2018); and one study each were on stages 2–5 (Yang et al., 2016), 3-4 (Holm et al., 2015) and 1-3 (Shigematsu et al., 2017). There were two studies that used other systems for classification of kidney function, including British National Formulary (BNF) (Shalini et al., 2013) and European Medicine Agency (EMA) (Nielsen et al., 2013) (Table.1).

3.4 Methods and resources used in identifying DRPs

Twelve studies have used only **the** chart review method to detect DRPs, either paper (Sweileh et al., 2007, Markota et al., 2009, Prajapati and Ganguly, 2013, Manjula Devi et al., 2014, Saleem and Masood, 2016, Saleem et al., 2017, Garedow et al., 2019) or electronic (Sheen et al., 2007, Yang et al., 2016, Taner et al., 2018, Nielsen et al., 2013, Won et al., 2018). Two studies involved patients interview in addition to chart review (Getachew et al., 2015, Juarez-Cedillo et al., 2016). Two studies used more than two methods (Holm et al., 2015, O'Shaughnessy et al., 2017). Information was not available in two studies (Gomez-Lobon et al., 2012, Sharif-Askari et al., 2014). In total, over thirty different prescribing guidelines or information sources were used to identify DRPs in the 20 studies. Seven studies used one source (Getachew et al., 2015, Nielsen et al., 2013, Prajapati and Ganguly, 2013, Saleem et al., 2017, Yang et al., 2016, Gomez-Lobon et al., 2012, Won et al., 2018). Nine studies used two or more sources (Holm et al., 2015, Manjula Devi et al., 2014, Markota et al., 2009, O'Shaughnessy et al., 2017, Shalini et al., 2013, Sharif-Askari et al., 2014, Sweileh et al., 2007, Sheen et al., 2007, Garedow et al., 2019). Two studies used combination of resources (Saleem and Masood, 2016, Juarez-Cedillo et al., 2016), whereas one study did not report (Taner et al., 2018). The most frequently used prescribing information sources were the BNF (n=4) (O'Shaughnessy et al., 2017, Saleem and Masood, 2016, Shalini et al., 2013, Sharif-Askari et al., 2014), the Renal Drug Handbook (RDH) (n=2) (Holm et al., 2015, O'Shaughnessy et al., 2017), and Micromedex, a collection of drug information databases (n=3) (Saleem et al., 2017, Manjula Devi et al., 2014, Gomez-Lobon et al., 2012), (Table 1).

3.5 Prevalence of DRPs

In the 20 studies, the prevalence of DRPs ranged from 12% to 87%. Figure 2 shows the proportion of patients with DRPs in those studies which reported the number of individual patients with drug errors. Two prospective studies using DRP as a defined outcome found a prevalence between 62 and 81% in 115 CKD patients (Holm et al., 2015, Garedow et al., 2019). One study reported ADRs only; this prospective observational study found that 11.7% of 154 participants with CKD stages 3 and 4 had experienced an ADR (Sharif-Askari et al., 2014). Adverse events were investigated in the secondary analyses of three Japanese trials, aimed to demonstrate the efficacy and safety of different doses of risedronate, and found 87% of 852 participants (CKD stages 1–3) experienced an adverse event (Shigematsu et al., 2017).

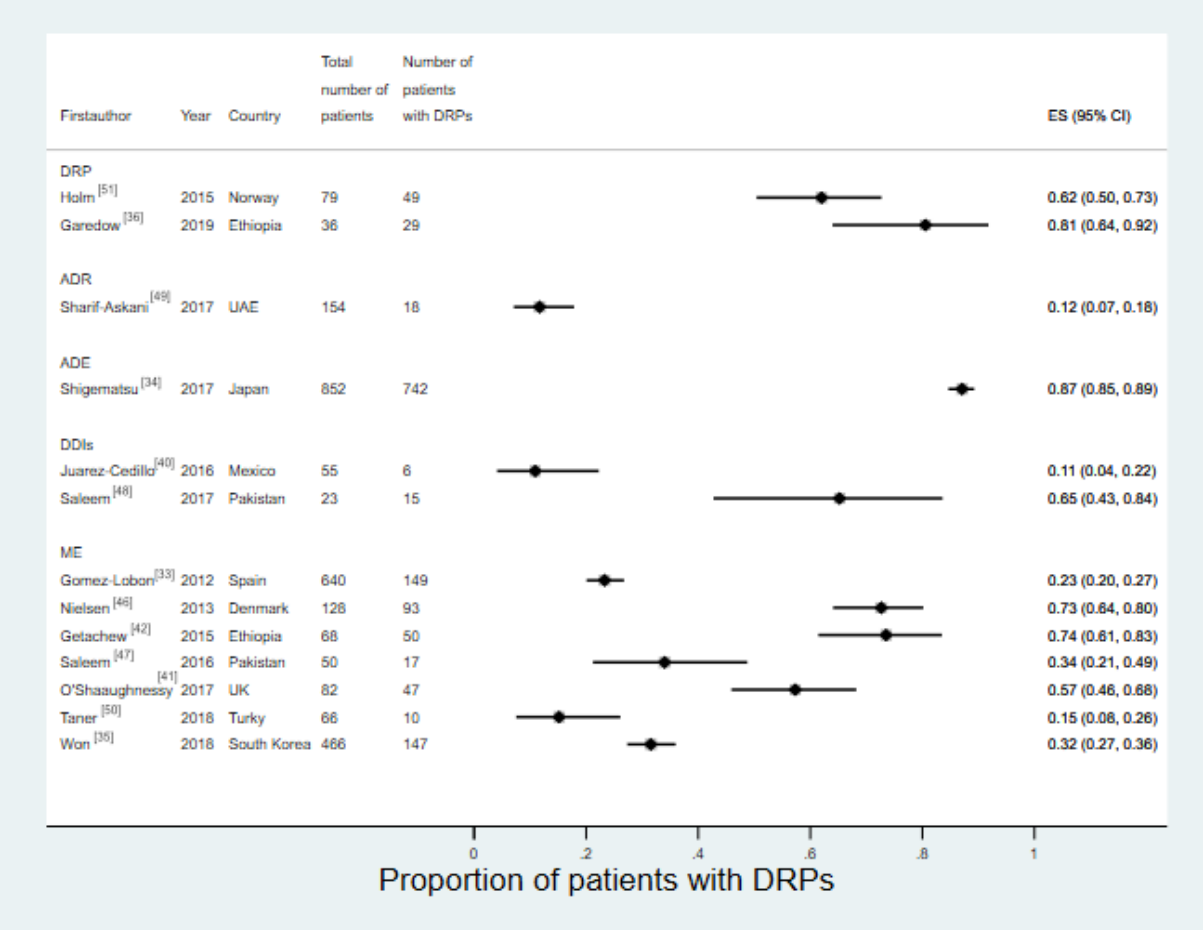

Figure 2: Proportion with drug-related problems (DRPs)

Potential drug–drug interactions (pDDIs) and drug–drug interactions (DDIs) were investigated retrospectively and prospectively in two studies. They used electronic databases in CKD stages 1–3 pDDIs, and three different sources in CKD stages 1–4 DDIs. The percentages of pDDIs and DDIs were 65% and 11%, respectively, in 109 CKD patients (Saleem et al., 2017, Juarez-Cedillo et al., 2016), (Table.2).

Most studies examined medication errors (n = 14) with 28,374 CKD patients, such as prescription and dosage problems at different CKD stages. One study focused on prescribing appropriateness and found that inappropriate prescription represented 15% of all prescriptions (1.27 per patient) in CKD stages 2–4 (Yang et al., 2016). Taner et al., 2018, measured lack of monitoring in 66 patients with renal impairment using metformin and found that 15% of the patients (10/66 patients) lacked monitoring, and 3% were using metformin while it was contraindicated in CKD stages 1–4, using a retrospective cross-sectional method (Taner et al., 2018), (Table 1).

Regarding dosing errors, four studies of 1306 CKD stage 3–4 patients found dosing errors at a prevalence of between 23.3 and 73.5% (Saleem and Masood, 2016, O'Shaughnessy et al., 2017, Gomez-Lobon et al., 2012, Getachew et al., 2015, Won et al., 2018).

Based on the number of drugs needing dose adjustment and the total number of patients, five studies found a range of 0.4–1.7 drugs needed dose adjustment per patient (4–17/10 patients) in 985 CKD stages 3 and 4 patients (Sweileh et al., 2007, Prajapati and Ganguly, 2013, Manjula Devi et al., 2014, Gomez-Lobon et al., 2012, Getachew et al., 2015), (Figure-3).

Inappropriate drug/dose and number of total drugs were reported in seven studies. Three studies found that 611 (15.6%) drugs were inappropriate out of 3900 total drugs

(range 40–343) in 752 CKD stage 3 and 4 patients (O'Shaughnessy et al., 2017, Manjula Devi et al., 2014, Gomez-Lobon et al., 2012) (figure-4). Sheen et al., 2007, found that 30% of mild to moderate renal impairment patients (28,374) were prescribed overdoses that required dose adjustment (Sheen et al., 2007). Shalini et al., 2013, found that 7% of antibiotic prescriptions needed dose adjustment in a mild stage of CKD (Shalini et al., 2013). The percentage of inappropriate drug dosage per total drugs ranged between 16.2% and 20.7% (1.2–1.4/patient) in CKD stage 3, but stage 4 prevalence could not be reported as the study did not differentiate between stage 4 and stage 5 (Markota et al., 2009, Nielsen et al., 2013). O'Shaughnessy et al., 2017, found that 86% of prescribed drugs in CKD stages 3 and 4 were potentially inappropriate prescribing (PIP) (O'Shaughnessy et al., 2017), (Figure-4) (Table.2).

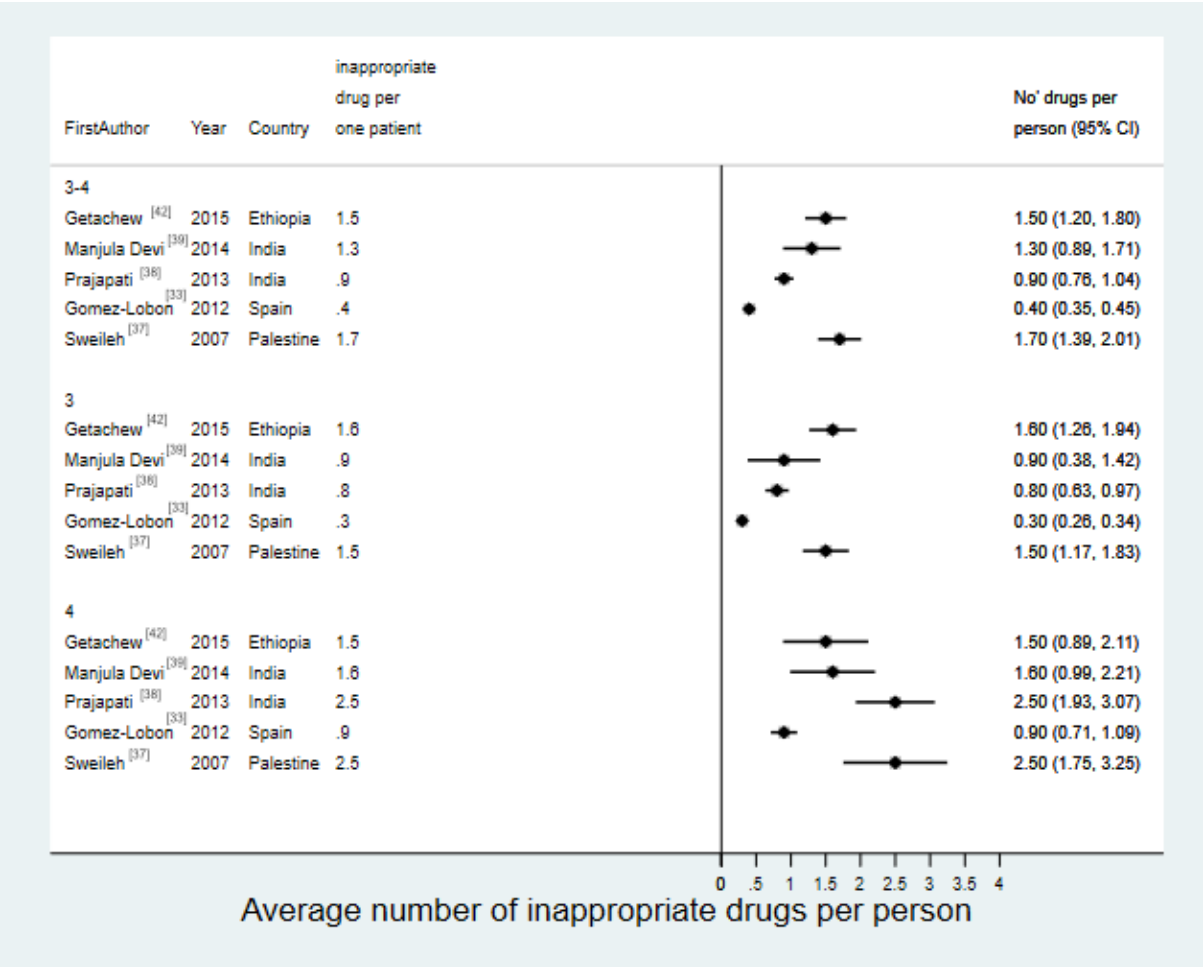

Figure 3: Average number of inappropriate drugs per person.

*Stages of CKD where 3-4 (CKD stages 3-4), 3 (CKD stage 3 only) and 4 (CKD stage 4 only)

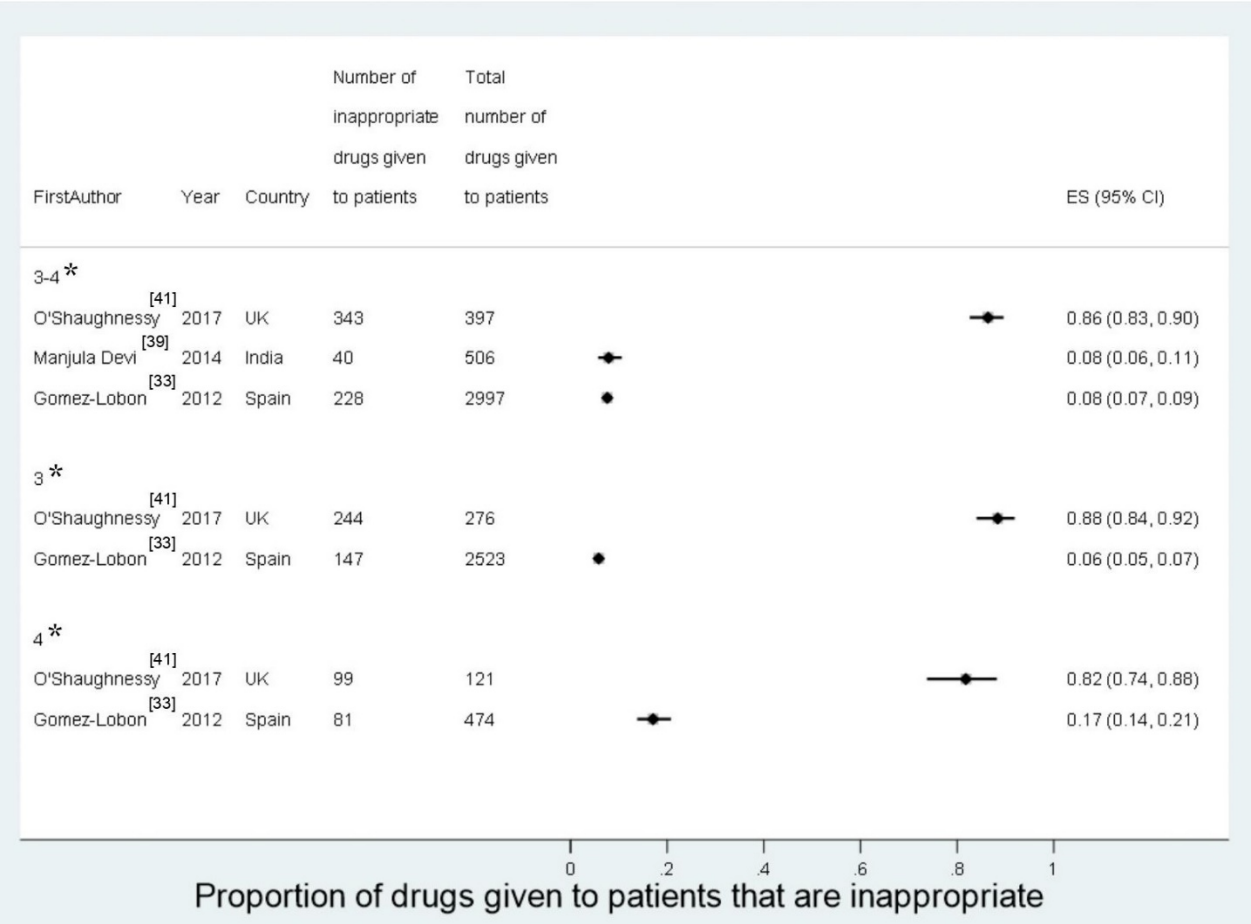

Figure 4: Proportion given inappropriate drugs.

*Stages of CKD where 3-4 (CKD stages 3-4), 3 (CKD stage 3 only) and 4 (CKD stage 4 only)

3.6 Most common drugs

From 12 studies that reported the most common drugs involved in DRPs for all included CKD stages (1–5), the drugs were antibiotics (O'Shaughnessy et al., 2017, Prajapati and Ganguly, 2013, Manjula Devi et al., 2014, Saleem and Masood, 2016, Gomez-Lobon et al., 2012), anticoagulants (Sharif-Askari et al., 2014), nutraceutical and electrolytes (Yang et al., 2016), H_2-antihistamines (cimetidine and ranitidine) (Getachew et al., 2015, Sheen et al., 2007), metformin (Won et al., 2018), statin (simvastatin) (Nielsen et al., 2013) and ferrous sulfate + omeprazole (Saleem et al., 2017). Three studies only reported common drugs for stages 1–4 CKD. The first reported that a combination of lysine clonixinate and dipyrone (metamizol) was the most common DDI in stage 4 CKD (Juarez-Cedillo et al., 2016). The second reported that the most frequently prescribed inappropriate drugs in patients with CKD stage 3 were ranitidine (71.4%) and digoxin (10.4%), with ranitidine (59.5%) and antibiotics (23.8%) most common in CKD stage 4 (Sweileh et al., 2007). In the third study, in CKD stage 3, a combination of ACE inhibitor and spironolactone was the most common drug needing dose adjustment, which represented 32.8% (Markota et al., 2009).

Holm et al., 2015, included only CKD stages 3 and 4 with metformin and benzylpenicillin being the most common drugs associated with 16 DRPs (Holm et al., 2015). One study reporting drug class instead of drug name found cardiovascular medication, gastrointestinal medication and analgesics were associated with DRPs (Garedow et al., 2019). Three studies investigated DRPs on a specific drug or class of drugs (metformin, risedronate, and antibiotics) (Shalini et al., 2013, Shigematsu et al., 2017, Taner et al., 2018).

Overall, antibiotics were the most common class of drugs cited as being involved in DRPs (21–80%), followed by the antihistamines cimetidine and ranitidine (11.4–67.2%), and oral antidiabetics (metformin) (Table 1)

Table 1: DRPs Characteristics in the Included Studies

Author & Year	Overall prevalence	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	CKD Stage 1-3	Other CKD classification	Method of detecting DRPs	Most common drugs
Drug-Related Problems									
Holm et al., 2015 (Holm et al., 2015)	62% of all participants had DRP (49 pts/79pts) 88DRP/49patients (1.5 DRP/pt)	Not included	Not included	90.5% (19 patients with DRP/21 total patients)	51.7% (30 patients with DRP/58 total patients)	-	-	NLH SPC Hospital GL RDH	Metformin
Garedow et al., 2019 (Garedow et al., 2019)	80.5% (29/36) patients had DRPs	-	-	-	-	80.5% (29/36) patients had DRPs	-	ESTG, 2014 UpToDate CPRPCHP KDIGO*, 2012 WHO guideline	Cardiovascular medications (31.9%). Gastrointestinal medication (19.1%). Analgesic (19.1%).

Author & Year	Overall prevalence	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	CKD Stage 1-3	Other CKD classification	Method of detecting DRPs	Most common drugs
Adverse Drug Reactions									
Sharif-Askari et al., 2014 (Sharif-Askari et al., 2014)	11.7% patient had ADR	Not included	Not included	9.4% patient had ADR	13.33% patient had ADR	-	-	ADET ADEME-DC And/or BNF 2012	Anticoagulant 70% (n = 44;) For all stages
Adverse Drug Events									
Shigematsu et al., 2017	87.08% patients had AE 742 AE in 852 patients (8.7/Patients)	82.82% patients had AE 82 AE in 99 patients	88% patients had AE 462 AE in 525 patients	86.8% patients had AE 198 AE in 228 patients	Not included	-	-	Based on the adverse event	Specific drug Study

Author & Year	Overall prevalence	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	CKD Stage 1-3	Other CKD classification	Method of detecting DRPs	Most common drugs
Drug-Drug Interactions									
Juarez-Cedillo et al., 2016 (Juarez-Cedillo et al., 2016)	10.9% patients had DDI	No DDI	No DDI	No DDI	66.66% (6 patients had DDI / 9 patients)	-	-	Combining three different sources: Stockley's drug interactions Hansten drug interactions Tatro drug interactions	Furosemide 22/273 (8.6%)
Saleem et al., 2017 (Saleem et al., 2017)	65.2% patients had PDDIs 15 PDDIs in 23 pts	-	-	-	Mixed with stage 5	65.2% patients had PDDIs 15 PDDIs in 23 pts	-	Micromedex	Ferrous sulfate + omeprazole 27(5.8%) General for all stages

Author & Year	Overall prevalence	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	CKD Stage 1-3	Other CKD classification	Method of detecting DRPs	Most common drugs
Medication Errors (All dosing Problems)									
Won et al,. 2018 (Won et al., 2018)	31.5% (147/466) patients had dosing errors.	-	-	26.3% (106/403) patients had dosing errors.	65% (41/63) patients had dosing errors.	-	-	Lexicomp Online®	Metformin (Frequency =38) Trimetazidine (Frequency =34) Ranitidine (Frequency =29)
O'Shaughnessy et al., 2017 (O'Shaughnessy et al., 2017)	57.32% (47/82) patients had PIP 86.4% drugs were inappropriate (343/397)	Not included	Not included	50.9% (28/55) patients had PIP 88.4% drugs were inappropriate (244/276)	70.4% (19/27) patients had PIP 81.8% drugs were inappropriate (99/121)	-	-	BNF RDH	Antibacterial for all stages (3-5)
Saleem et al., 2016 (Saleem and Masood, 2016)	34% patients with unadjusted drug dose (17/50)	Not included	Not included	26.3% (5/19)	38.7% (12/31)	-	-	**Adopted from:** BNF-58 DPRF-2007 DPRF1983	Antibiotics For all stages

Author & Year	Overall prevalence	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	CKD Stage 1-3	Other CKD classification	Method of detecting DRPs	Most common drugs
								DDEP-CKD	
Yang et al., 2016 (Yang et al., 2016)	15.33% Inappropriate Prescriptions of all prescriptions [233 IP /183 patients (1.3/patient)]	Not Included	12% IP of all prescriptions 21IP/29 patients	13.05% IP of all prescriptions 118 IP / 110 patients	21.3% IP of all prescriptions 94 IP / 440 Patients	-	-	Medication instruction approved by the China Food and Drug Administration	Nutraceutical and electrolytes And Metformin For all patients
Getachew et al., 2015 (Getachew et al., 2015)	105 drugs need adjustment /68 patients (1.5/patients) 73.5% of patients had dosing problems (50/68)	Not included	Not included	83 drugs need adjustment /53 patients (1.6/patients) 73.6% of patients had dosing problems (39/53)	22 drugs need adjustment /15 patients (1.5/patients) 73.3% of patients had dosing problems (11/15)	-	-	DPRFAC-2007	Cimetidine --> 3/18 (16.7%) were IDDA
Manjula Devi et al., 2014 (Manjula Devi et al., 2014)	7.9% drugs need dose adjustment (40/506) 40 drug need adjustment in 30 patients (1.3/patient)	No results	No results	2.3% drugs need dose adjustment (12/40) 12 drug need adjustment in 13 patients	5.5% drugs need dose adjustment (28/40) 28 drug need adjustment in 17	-	-	Micromedex drug information (V2.00.000) TD	Antibiotics (39.77%)

Author & Year	Overall prevalence	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	CKD Stage 1-3	Other CKD classification	Method of detecting DRPs	Most common drugs
					patients (1.6/patient)			AHFS	
Prajapati et al., 2013 (Prajapati and Ganguly, 2013)	154 inappropriate drugs in 178 patients	Not included	Not included	93 drugs need dose adjustment in 113 patient (all stage 3 patients)	61 drugs need dose adjustment in 27 patient 2.3/patient (all stage 4 patients)	-	-	DPRF-DG	Antimicrobials (n = 144, 80%) for all stages
Gomez-Lobon A, 2012 (Gomez-Lobon et al., 2012)	23.3% (149/640) patients with non-adjusted medication 7.6% drugs needed adjustment of 2997 total drugs	-	-	18.6% (102/547) patients with non-adjusted medication. 147 interventions /102 patients (1.4) 147 Drugs needed adjustment /2523 total drugs (5.8%)	50.5% (47/93) patients with non-adjusted medication. 81 interventions /47 patients (1.7) 81 Drugs needed adjustment /474 total drugs (17%)	-	-	Micromedex	Antibiotic (45%) Prokinetics (10%) NSAIDs (7%) Opioids (7%)

Author & Year	Overall prevalence	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	CKD Stage 1-3	Other CKD classification	Method of detecting DRPs	Most common drugs
Sweileh et al., 2007 (Sweileh et al., 2007)	119 TEM needed dose adjustment/ 69 patients (1.7 / patient)	Not included	Not included	77 TEM needed dose adjustment among 52 patients (1.5/patient)	42 TEM needed dose adjustment among 17 patients (2.5/patient)	-	-	PDR DIH	Stage 3: Ranitidine (n=55, 71.4%) Stage 4: Ranitidine (n=25, 53.5%)
Taner et al., 2018 (Taner et al., 2018)	Lack of monitoring (10/66) 15.2% of patients	-	-	-	Contraindicated in 2 patients	-	-	Not mentioned	Specific drug Metformin
Shalini et al., 2013 (Shalini et al., 2013)	7% antibiotic needed dose Adjustment (78/1119) 78 antibiotics need dose adjustment in 34 patients (2.3/patient)	-	-	-	-	-	Mild: 7% antibiotic needed dose Adjustment (78/1119) 78 antibiotics need dose adjustment in 34 patients (2.3/patient)	BNF PPC In case of differences BNF were accepted.	Gentamicin (46 pts)
Nielsen et al., 2013. (Nielsen et al., 2013)	20.8% inappropriate drugs (180/867)	Not included	Not included	20.76% inappropriate drugs (180/867)	Mixed with stage 5	-	-	Renbase	Simvastatin (13 patients)

Author & Year	Overall prevalence	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	CKD Stage 1-3	Other CKD classification	Method of detecting DRPs	Most common drugs
	180 ID in 93 patients (1.9/pt) of 128 total patients (1.4/patient) 72.65% patient had Inappropriate drug dose (93/128)			180 ID in 93 patients (1.9/pt) of 128 total patients (1.4/patient) 72.65% patient had Inappropriate drug dose (93/128)					
Markota et al., 2009 (Markota et al., 2009)	142 drug need adjustment in 122 patients (1.2/patient) 142/874 (16.2%) drugs were inappropriate	Not included	Not included	142 drug need adjustment in 122 patients (1.2/patient) 142/874 (16.2%) drugs were inappropriate	Mixed with stage 5	-	-	MI If not clear DGA	Stage 3: Combination of ACE inhibitor and Spironolactone (32.8%) Digoxin (28.4%) and Metformin (20.9%)
Sheen et al., 2007 (Sheen et al., 2007)	30.2% overdosed for normal - moderate	-	-	-	-	-	Normal --> 1.1% Mild --> 1.3% Moderate- >27.8%	RDD SGAT	Ranitidine 11092/97138 prescriptions (11.4%)

Author & Year	Overall prevalence	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	CKD Stage 1-3	Other CKD classification	Method of detecting DRPs	Most common drugs

ADEME-DC; Adverse drug events and medication errors: detection and classification methods (2004). **ADET**; Adverse drug event trigger tool: a practical methodology for measuring medication related harm (2003). **ADR**; Adverse Drug Reaction. **AE**; Adverse Events. **AHFS**; American Hospital Formulary Service Drug Information. American Society of Health System. Pharmacol. USA. 2009. **BNF**; British National Formulary. **CPRPCHP**; Clinical Practice Recommendations for Primary Care Physicians and Health care. **DDEP-CKD**; Drug Dosing in Elderly Patients with Chronic Kidney Disease guidelines by Lassiter et al. **DDIs**; Drug-Drug Interactions. **DIH**; Drug Information Handbook. **DGA**; Dosing guideline for adults 4th edition. **DPRF**; Drug Prescribing in Renal Failure: Dosing Guidelines for Adult. **DPRFAC**; Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children (Aronoff et al., 2007). **DPRF-DG**; Drug prescribing in renal failure – dosing guidelines for adults, 4th edition. **DRP**; Drug-Related Problems. **ESTG**; Ethiopian Standard Treatment Guideline, 2014. **ID**; Inappropriate Drug. **IP**; Inappropriate prescriptions. **KDIGO**; Kidney Disease Improving Global Outcomes, Clinical Practice Guideline, 2012. **MI**; Manufacturer instructions. **NLH**; Norsk legemiddelhåndbok ; 2010. **pDDIs**; Potentially Drug-Drug Interactions. **PDR**; physician disk reference. **PIP**; Potentially Inappropriate prescriptions. **PPC**; pharmaceutical product catalogue. **RDD**; Renal Dosing Database. **RDH**; Renal Drug Handbook. **SGAT**; Sanford Guide to Antimicrobial Therapy 34th edition (2004). **SPC**; Summary of Product Characteristics. **TD**; Therapeutic Drugs (Colin Dollery) Churchill Livingston; Edinburgh. 1999. Vol 1. **TEM**; drugs that are nephrotoxic, excreted, or metabolized (medications) by the kidney. **WHO**; World Health Organisation.

*Clinical Practice Guideline.

3.7 Risk Factors

Risk factors for DRPs were reported in 10 studies. The degree of renal impairment was the most common associated factor in the occurrence of DRPs in seven studies (Yang et al., 2016, Sheen et al., 2007, Sharif-Askari et al., 2014, Saleem and Masood, 2016, Holm et al., 2015, Sweileh et al., 2007, Garedow et al., 2019). This was followed by the number of medications in six studies(Sharif-Askari et al., 2014, Saleem et al., 2017, Saleem and Masood, 2016, Holm et al., 2015, Garedow et al., 2019, Won et al., 2018), age in three studies (Sweileh et al., 2007, Saleem et al., 2017, Won et al., 2018), length of hospitalisation longer than 5 days in two studies (Saleem et al., 2017, Prajapati and Ganguly, 2013), and gender in two studies (Sweileh et al., 2007, Holm et al., 2015). Other risk factors are listed in Table 2.

Table 2: Risk factors for DRPs

Risk Factors	Holm et al., 2015 (Holm et al., 2015)	Sharif-Askari et al., 2014 (Sharif-Askari et al., 2014)	Saleem, et al., 2017 (Saleem et al., 2017)	Yang et al., 2016 (Yang et al., 2016)	Prajapati et al., 2013 (Prajapati and Ganguly, 2013)	Sheen et al., 2007 (Sheen et al., 2007)	Saleem et al., 2016 (Saleem and Masood, 2016)	Sweileh et al., 2007 (Sweileh et al., 2007)	Garedow et al., 2019 (Garedow et al., 2019)	Won et al,. 2018 (Won et al., 2018)	Total
1. Patient's GFR/ Kidney function	√	√		√		√	√	√	√		7
2. Number of medication	√	√					√			√	4
3. Number of prescribed drugs ≥5			√						√		2
4. Age								√		√	2
5. Age < 60 years			√								1
6. gender	√							√			2
7. Length of hospitalisation ≥ 5 days			√		√						2
8. Presence of a comorbidity such as hypertension			√								1
9. Number of drugs requiring dosing adjustments in patients with renal impairment										√	1
10. Prescribers' poor knowledge of medications requiring dosage adjustment				√							1
11. Lack of evidence-based data to guide prescribers on dosage adjustments as well as lack of quantitative data in the available MI.29,30				√							1
12. Underestimation of potential adverse events				√							1
13. Lower serum level of albumin		√									1
14. Vascular Disease		√									1
15. Higher serum level of CRP		√									1
16. Physician's quantity of prescriptions						√					1
17. Clinical experience of physicians						√					1
18. the presence of a comorbidity, such as hypertension							√				1
19. the presence of ≥5 comorbidity									√		1
20. Marital status (Married).									√		1
TOTAL	3	5	4	4	1	3	3	3	4	3	33

4. Discussion

To our knowledge, this is the first systematic review to examine the prevalence of DRPs among hospitalised patients with CKD (range 12–87%), the risk factors associated with occurrence of DRPs and the most common drugs involved in DRPs. Our review found only one study on ADRs and one on ADEs with prevalence of 12% and 87%, respectively. However, there were 14 studies that investigated MEs based on inappropriate prescriptions and dosing errors.

4.1 Medication errors

There is a widespread occurrence of medication errors in CKD patients, in line with a 2004 systematic review investigating clinical pharmacists' activity in CKD patients (Stemer and Lemmens-Gruber, 2011). We found a range of 0.4–1.7 medication errors per patient, with around one in six drugs used in CKD patients deemed inappropriate in the five studies that reported this (Getachew et al., 2015, Gomez-Lobon et al., 2012, Manjula Devi et al., 2014, Prajapati and Ganguly, 2013, Sweileh et al., 2007). We found 23.3–73.5% of CKD patients had dosing problems, similar to that found in a previous review (Long et al., 2004). Inappropriate prescriptions were reported in one study with 15% of prescriptions having such errors (Yang et al., 2016). However, a previous systematic review reported that prevalence ranged from 9.4 to 81.1% in hospitalised CKD patients (Tesfaye et al., 2017). This wide range could be due to several factors such as error identification methods and population. Clearly, greater focus on ensuring prescribers can prescribe appropriately for CKD patients is required.

4.2 Renal function reporting

Choice of an appropriate drug and dosage for patients with CKD depends on the renal function of the patients. Although there is no gold standard to estimate kidney function, there are several methods/equations such as MDRD, CG and Chronic Kidney

Disease—Epidemiology Collaboration (CKD-EPI) (Jones, 2011, Karsch-Volk et al., 2013). In this systematic review, CG and MDRD were presented in 16 studies, which recommended their use in clinical practice (Levey et al., 2003, Poggio et al., 2005). However, the accuracy of the above-mentioned equations among different patient groups remains questionable (Trinkley et al., 2014, Khanal et al., 2017, Lessard and Zaiken, 2013). In obese or elderly multi-ethnic patients, using CG and MDRD can provide conflicting estimations of GFR leading to incorrect dosage recommendations. The US National Kidney Disease Education Program (NKDEP) 2015 recommends use of creatinine clearance or estimated GFR based on body surface area (BSA) normalisation removed for drug dosage, such as narrow therapeutic window drugs (Drion et al., 2011, Jones, 2011, Park et al., 2012, Gill et al., 2007, National Kidney Disease Education Program, 2015). Overall, the choice of estimating method has an impact on dose adjustment requirement, and this should be considered both in clinical practice by prescribers and in study design (Dowling et al., 2013, Hoffmann et al., 2016, The National Institute of Diabetes and Digestive and Kidney Diseases, 2015).

4.4 Criteria for CKD diagnosis

The criteria for CKD diagnosis is the presence of reduced GFR or one or more kidney damage markers, such as structural abnormalities detected by imaging or urine sediment abnormalities (Levin et al., 2013). Only three studies followed this criterion, either by a review of SCr levels by measuring GFR or by finding CKD diagnosis in the patients' files (Juarez-Cedillo et al., 2016, O'Shaughnessy et al., 2017, Garedow et al., 2019). Researchers focusing on CKD patients should consider this criterion to avoid mixing acute kidney injury (AKI) with CKD.

4.5 Identification of DRPs

Many methods for identifying DRPs have been used in the literature, such as chart review, direct observation and incident reports, and each of these methods has advantages and disadvantages (Manias, 2013, Meyer-Massetti et al., 2011). In this systematic review, most of the studies (60%) used chart review (paper or electronic) in order to detect DRPs (Sheen et al., 2007, Sweileh et al., 2007, Markota et al., 2009, Nielsen et al., 2013, Prajapati and Ganguly, 2013, Manjula Devi et al., 2014, Saleem and Masood, 2016, Yang et al., 2016, Saleem et al., 2017, Taner et al., 2018, Won et al., 2018, Garedow et al., 2019). This method is considered better for identifying DRPs, but does identify DRPS of low clinical significance (Grasso et al., 2003, Manias, 2013). Six studies in this systematic review used a combination of two or more methods, such as chart review with computer system (Shalini et al., 2013, Sharif-Askari et al., 2014, Getachew et al., 2015, Juarez-Cedillo et al., 2016, O'Shaughnessy et al., 2017, Shigematsu et al., 2017).

4.6 Drug Dosage Guidelines in CKD

Many guidelines are available in the literature for drug dosage in patients with CKD. In this systematic review, 31 different drug dosage guidelines were used. There are significant differences in the definitions of CKD stages and the drug dosage recommendations of such guidelines (Vidal et al., 2005). Khanal et al., 2014, reviewed five CKD drug dosage sources and reported that only slight agreement was found amongst them (Khanal et al., 2014). A study that investigated the agreement between two references (BNF and RDH) found variations across stages of CKD, medicine classes, and hospital care phases (O'Shaughnessy et al., 2017). Similarly, definition and CKD classification were found to be different among the five sources reviewed by

Khanal et al., 2014 (Khanal et al., 2014). These differences could affect the reporting of DRPs among studies

3.7 Most common drugs involved in DRPs

The included studies reported a wide range of medications associated with DRPs. Some studies focused on specific drugs or drug classes in order to achieve a specific goal (Dalrymple and Go, 2008, Shalini et al., 2013, Shigematsu et al., 2017, Taner et al., 2018). Three studies investigated a specific group of drugs that are excreted renally or have a renal effect (Gomez-Lobon et al., 2012, Manjula Devi et al., 2014, Sweileh et al., 2007). Overall, in this review, antibiotics, antihistamines and oral antidiabetics represented the most common drug classes involved in DRPs. High rates of infections in CKD patients may explain the presence of antibiotics in these studies (Dalrymple and Go, 2008, Ishigami and Matsushita, 2019).

It was found that 32–56% of hospitalised CKD patients have at least one potentially inappropriate drug (Doody et al., 2015, Chang et al., 2015). Pharmacokinetic changes in CKD patients makes drug optimisation complex and increases the DRP risks compared with those without CKD (Roberts et al., 2018, Lea-Henry et al., 2018). Therefore, prescribers should pay more attention in these populations to avoid adverse effects and further kidney injury. Antihistamines presented as the most common class in three studies, with the problem being that these medications are excreted through the kidney, and in CKD patients they will accumulate in the blood resulting in different problems such as mental state alteration and raised liver enzymes (Manlucu et al., 2005). Therefore, their dosage should be reduced with reduced renal function.

Metformin can cause serious and life-threatening ADRs (mortality rate of 25–50%) in renal patients (Defronzo et al., 2016, Inzucchi et al., 2014, Vecchio et al., 2014), and

was mentioned in six studies. Metformin was found to be common in DRPs identified in this review in hospital settings (Tesfaye et al., 2017). Renal function should be monitored before and during metformin therapy. One study reported that 11.7% of patients had an ADR, with anticoagulants (heparin, enoxaparin and warfarin) being associated with the majority (70%) of such ADRS (Sharif-Askari et al., 2014). Anticoagulants can increase the risk of severe haemorrhage by 4.9-fold in renal dysfunction (Yao et al., 2017).

4.8 Risk factors section

Degree of renal function impairment was the most common risk factor found in seven studies of this review (Yang et al., 2016, Sweileh et al., 2007, Sheen et al., 2007, Sharif-Askari et al., 2014, Saleem and Masood, 2016, Holm et al., 2015, Garedow et al., 2019). This finding is in line with DRPs in CKD patients in the prior literature (Tesfaye et al., 2017, Peterson and Gustafsson, 2017).

The number of prescribed medicines (Won et al., 2018, Sharif-Askari et al., 2014, Saleem et al., 2017, Saleem and Masood, 2016, Holm et al., 2015, Garedow et al., 2019) was the next most common risk factor, as found in previous reviews (Tesfaye et al., 2017). Polypharmacy is linked to higher risk for DRPs. Careful deprescribing (which means “the systematic process of identifying and discontinuing drugs in instances where existing or potential harm outweigh existing, or potential, benefit” (Scott et al., 2015), of unnecessary medication could help to minimise the risk of DRPs in CKD patients (Scott et al., 2015, Kantor et al., 2015). However, prescribers should pay equal attention when prescribing new medication to CKD patients, taking into account degree of CKD and the patient response to new medication (Whittaker et al., 2018).

4.9 Strengths and Limitations

To the best of our knowledge, this is the first systematic review conducted to review the available literature on DRPs in hospitalised patients with CKD stages 1–4. Previous systematic reviews included studies on non-hospitalised patients (Dorks et al., 2017), or hospitalisation related to drugs. This study used a comprehensive search strategy to find eligible articles from eight databases, with no country restrictions, and included the reference lists of the included studies and potential relevant systematic reviews. Furthermore, the protocol was prepared based on PRISMA-P standards and registered in PROSPERO.

Direct comparison between studies was limited and meta-analysis not performed due to clinical and methodological heterogeneity. Limited data were available on CKD stages 1 and 2, as some studies included the two stages, but did not report DRPs for these stages.

4.10 Implications for Practice and research

This systematic review showed that DRPs, especially drug dosage problems, are common in hospitalised patients with CKD. Healthcare organisations should pay attention to this population given the effect DRPs have on mortality, morbidity and healthcare costs (Rozich and Resar, 2001, Ruths et al., 2007, Wester et al., 2008). Recognising risk factors facilitates identifying patients at risk for DRPs and could be used to determine which patients are at risk for occurrence of DRPs. Efforts to establish a uniform guideline for CKD patients for estimating renal function, and deciding the drug and dose, could also help avoid DRPs.

Future well designed prevalence studies of DRPs in hospitalised CKD patients to capture related risk factors to allow prevention, monitoring and early intervention are needed. Educational packages on prescribing in CKD to raise awareness of the risk

of DRPs, as well as the use of assessment tools may help patients avoid unwanted treatment outcomes (Urbina et al., 2014). The different guidelines and differing methods of estimating renal function suggest a need for evidence-based guidelines for patients with CKD (Tesfaye et al., 2017, Khanal et al., 2014). A uniform guideline for CKD/renal impairment patients is needed to avoid drug dosage problems and subsequent DRPs.

5. Conclusion

Our systematic review found a high prevalence of drug-related problems in hospitalised patients with CKD; however, the range was variable across the studies. The most common prescribing problem is related to drug dosage, with the most common drugs involved being antibiotics, H2-antihistamines and oral antidiabetic drugs (metformin). The severity of renal impairment, increased number of drugs and age were the most significant risk factors for DRPs. Future studies on the prevalence of DRPs in CKD should use agreed definitions of DRPs and standard estimations of renal function.

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Appendixes:

1- Search strategy

2- Quality assessment

1. Search Strategy

Searches	Search terms
1	exp "Drug-Related Side Effects and Adverse Reactions"/
2	exp Inappropriate Prescribing/
3	exp Medication Errors/
4	exp Adverse Drug Reaction Reporting Systems/
5	(drug-related problem* or medicine-related problem* or medication-related problem*).ti,ab.
6	adverse drug event*.ti,ab.
7	adverse drug reaction*.ti,ab. medication error*.ti,ab.
8	(inappropriate prescri* or inappropriate medication*).ti,ab.
9	(drug-related complication* or medicine-related complication* or medication-related complication*).ti,ab.
10	("drug-therapy problem*" or "drug therapy problem*").ti,ab.
11	("ADR" or "ADE" or "DRP" or "MRP").ti,ab.
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	exp Renal Insufficiency, Chronic/
14	*Renal Insufficiency, Chronic/
15	exp Glomerular Filtration Rate/
16	("chronic kidney disease*" or "chronic renal disease*" or "kidney disease*" or "renal disease*" or "chronic renal insufficienc*" or "chronic kidney insufficienc*" or "renal insufficienc*" or "kidney insufficienc*" or "impaired kidney function*" or "impaired renal function*" or "renal impairment*" or "kidney impairment*" or "glomerular filtration rate" or "GFR" or "CKD").ti,ab.
17	13 or 14 or 15 or
18	exp INPATIENTS/
19	exp Patient Admission/
20	("hospital patient*" or "hospital inpatient*" or "hospital in-patient*" or "inhospital patient*" or "in-hospital patient*" or "hospitali?ed patient*" or "hospitali?ed").ti,ab.
21	18 or 19 or 20
22	12 AND 17 AND 21

2- Quality assessment scores of the included studies.

Studies Assessment	**Q1:** Was the sample frame appropriate to address the target population?	**Q2:** Were study participants sampled in an appropriate way?	**Q3:** Was the sample size adequate?	**Q4:** Were the study subjects and the setting described in detail?	**Q5:** Was the data analysis conducted with sufficient coverage of the identified sample?	**Q6:** Were valid methods used for the identification of the condition?	**Q7:** Was the condition measured in a standard, reliable way for all participants?	**Q8:** Was there appropriate statistical analysis?	**Q9:** Was the response rate adequate, and if not, was the low response rate managed appropriately?	**Overall Appraisal**
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	**Overall Appraisal**
Holm et al., 2015	Y	Y	N	Y	Y	Y	Y	Y	Y	I
Garedow et al., 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
Sharif-Askari et al., 2014	Y	Y	N	Y	Y	Y	Y	Y	Y	I
Shigematsu et al., 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
Juarez-Cedillo et al., 2016	N	Y	N	Y	Y	Y	Y	N	Y	I
Saleem, et al., 2017	Y	Y	N	Y	Y	Y	Y	Y	Y	I
Won et al., 2018	N	Y	Y	Y	Y	Y	Y	Y	Y	I

Studies Assessment	**Q1:** Was the sample frame appropriate to address the target population?	**Q2:** Were study participants sampled in an appropriate way?	**Q3:** Was the sample size adequate?	**Q4:** Were the study subjects and the setting described in detail?	**Q5:** Was the data analysis conducted with sufficient coverage of the identified sample?	**Q6:** Were valid methods used for the identification of the condition?	**Q7:** Was the condition measured in a standard, reliable way for all participants?	**Q8:** Was there appropriate statistical analysis?	**Q9:** Was the response rate adequate, and if not, was the low response rate managed appropriately?	**Overall Appraisal**
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	**Overall Appraisal**
O'Shaughnessy et al., 2017	N	Y	N	Y	Y	Y	Y	Y	Y	I
Saleem et al., 2016	Y	Y	N	Y	Y	Y	Y	Y	Y	I
Yang et al., 2016	N	Y	N	Y	Y	Y	Y	N	Y	I
Getachew et al., 2015	N	Y	N	Y	Y	Y	Y	Y	Y	I
Manjula Devi et al., 2014	N	Y	N	Y	Y	Y	Y	N	Y	I
Prajapati et al., 2013	N	Y	N	Y	Y	Y	Y	Y	Y	I
Gomez-Lobon, 2012	Y	Y	Y	Y	Y	Y	Y	N	Y	I
Sweileh et al., 2007	N	Y	N	Y	Y	Y	Y	Y	Y	I

Studies Assessment	**Q1:** Was the sample frame appropriate to address the target population?	**Q2:** Were study participants sampled in an appropriate way?	**Q3:** Was the sample size adequate?	**Q4:** Were the study subjects and the setting described in detail?	**Q5:** Was the data analysis conducted with sufficient coverage of the identified sample?	**Q6:** Were valid methods used for the identification of the condition?	**Q7:** Was the condition measured in a standard, reliable way for all participants?	**Q8:** Was there appropriate statistical analysis?	**Q9:** Was the response rate adequate, and if not, was the low response rate managed appropriately?	**Overall Appraisal**
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	**Overall Appraisal**
Taner et al., 2018	Y	Y	N	Y	Y	Y	Y	Y	Y	I
Shalini et al., 2013	Y	Y	N	Y	Y	Y	Y	N	Y	I
Nielsen et al., 2013.	Y	Y	N	Y	Y	Y	Y	N	Y	I
Markota et al., 2009	Y	Y	N	Y	Y	Y	Y	N	Y	I
Sheen et al., 2007	Y	Y	Y	Y	Y	Y	Y	N	Y	I

Abbreviations:

Y: Yes; **N**: No; **U**: Unclear; **NA**: Not Applicable; **I**: Include; **E**: Exclude; **S**: Seek Further Information