SUPPLEMENTAL APPENDIX

Table of Contents

Medication Safety in Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD): Delphi Panel Round 1

Background

Patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD) are at increased risk of adverse events due to the nephrotoxic effects of drugs and/or inappropriate drug dosing, particularly of those drugs that rely on kidney function for elimination. This patient population often represents an older demographic, who are taking multiple medications for multiple comorbidities. It is difficult for primary care providers to easily access a list of commonly prescribed, potentially harmful medications in those patients with CKD or ESRD. The development of such a list would contribute to an effective strategy to reduce and prevent harm to patients with CKD.

Purpose

Develop a list of commonly prescribed, potentially harmful medications in patients with CKD or ESRD that:

1. reduces the risk of nephrotoxic effects in patients with decreased kidney function
2. provides recommendations on dosing for medications which should be adjusted or avoided in patients with decreased kidney function

Instructions:

1. A supplementary resource has been provided in your e-mail, entitled [*insert name here*] which includes for each medication a summary [recommended dosing, adverse effects, contraindications, drug interactions and pharmacokinetics], and source materials to help guide you through the questions.
2. There will be an opportunity at the end of the questionnaire to add medications which you believe are important for consideration and have not been included. These will be reviewed in a subsequent round of the ORN Medication Safety working group. Feel free to provide any relevant references.
3. For each medication in the questionnaire, there will be two tables side by side, one for dose adjustment and one for dose avoidance. Please complete both of these.
4. If you feel that a drug requires dose adjustment or avoidance at lower levels of kidney function, simply indicate the highest eGFR range provided at which you think that should occur. If for example you feel that a drug should be adjusted or avoided at any eGFR value less than 60 ml/min/m^2, indicate this by selecting an eGFR level [e.g. 45-59 ml/min/m^2]. All eGFR values below that range will be automatically completed for you.

The aggregated results of this survey will be returned to you for your review within **two weeks** of the survey completion date [*insert date here*]. The second round will be on [*insert date here*].

Please Note: Although creatinine clearance has been used historically to evaluate kidney function for clinical and pharmacokinetic studies, eGFR is now the commonly used method to estimate kidney function, is familiar to primary care providers, and has been evaluated with respect to medication dosing, safety and efficacy. With that in mind, and after much discussion, it has been decided that eGFR, rather than creatinine clearance, will be used as the preferred kidney function measure in the proposed work.

Instructions for the Consensus Workshop members

CKD Medication Safety: Focus Group Guide

April 24th, 2018

8:30 AM to 3:00 PM

Background

Patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD) are at increased risk of adverse events due to the nephrotoxic effects of drugs and/or inappropriate drug dosing, particularly of those drugs that rely on kidney function for elimination. This patient population often represents an older demographic, who are taking multiple medications for multiple comorbidities. It is difficult for primary care providers to easily access a list of commonly prescribed, potentially harmful medications in those patients with CKD or ESRD. The development of such a list would contribute to an effective strategy to reduce and prevent harm to patients with CKD.

Over the last year, the ORN conducted a literature review to identify high-risk medications, and then obtained consensus from a group of experts (i.e. Delphi panel members) through a series of questionnaires; the Delphi Panel recommended 16 medications on the list to be avoided and 63 medications to be dose adjusted in patients with CKD or ESRD.

Use of Information

The information collected throughout this study and focus group will inform the following:

1. Development of a concise, pragmatic list of medications to be adjusted or avoided among patients with CKD or ESRD.

2. Development of knowledge translation tools (e.g., educational materials, publications, conference presentations and posters) targeted at Primary Care Providers and Pharmacists to reduce adverse drug events among patients with CKD or ESRD.

Focus Group Discussion Guide

- **Facilitator's welcome, introduction and instructions to participants**
- **Provide CCO Volunteer Agreement Form and ensure it is completed (if not already completed prior to focus group date)**

Welcome and thank you for volunteering to take part in this focus group. You have been asked to participate as your point of view is important. I realize you are busy and I appreciate your time.

Introduction

We would like to convene a smaller group of experts to help us prioritize the list of medications which are most relevant for primary care providers. You are being invited to take part in this focus group because you have been identified as having an important perspective in this area.

This focus group discussion will take approximately 6 hours, with time allocated for a break and lunch.

Purpose and Materials

This focus group discussion is designed to assess your opinions about medications which have been identified to require dose-adjustment or avoidance in patients with renal impairment.

The purpose of this focus group is to provide general recommendations on the medications which may cause the most serious Adverse Events (AE) and are used in Primary Care setting (Family Physicians, Emergency Departments, Long Term Care, etc.)

You will be provided a list of these medications, along with the recommendations produced by the Delphi Panel. You will be provided with the preliminary recommendations produced by the members of this focus group, including yourself. You will also be provided with supplementary information from the Compendium of Pharmaceuticals and Specialties (CPS), where available.

You will be asked to support the grouping of these medications with consideration for those causing the most severe harm to the least. The goal of the group to create and prioritize a final grouping of medications that must be dose-adjusted and/or avoided in patients with renal impairment.

Anonymity

I would like to assure you that the discussion will be anonymous. The notes taken during the course of the focus group will contain no information that would allow individual subjects to be linked to specific statements. You should answer and comment as accurately and truthfully as possible. I and the other focus group participants would appreciate it if you would refrain from discussing the comments of other group members outside the focus group. If there are any questions or discussions that you do not wish to answer or participate in, you do not have to do so; however please try to answer and be as involved as possible.

Ground rules

- The most important rule is that only one person speaks at a time.
- There are no right or wrong answers
- You do not have to speak in any particular order
- When you do have something to say, please do so. There are many of you in the group and it is important that I obtain the views of each of you

- You do not have to agree with the views of other people in the group
- Does anyone have any questions or want to add any ground rules?
- OK, let's begin

Round of Introductions

- Focus group members and ORN staff to introduce one another around the table

Introductory Question [30 minutes]

I am going to provide you with a few minutes to review the medication list and think about your experience of providing care to renal patients, and any experiences you have learned from when prescribing the medications currently on the list of medications to avoid or dose-adjust. I will also provide an overview of the group results from the preliminary medication safety survey. Does anyone have any initial thoughts?

Guiding Questions

1. **How often do you see this medication prescribed in community practice?**

2. **How severe are the Adverse Event's associated with this medication if it is <u>NOT</u> dose-adjusted or avoided among renal patients?**

3. **What are the Adverse Event's associated with this medication if it is <u>NOT</u> dose-adjusted or avoided among renal patients?**

Fundamental Question [5.5 hours, including a 45 minute lunch and two 15 minute breaks]

4. **Would you include this medication in a final list to be provided to primary care providers highlighting medications which must be avoided or dose-adjust among patients with renal impairment?**

Table S1. Medication list considered by Delphi panel		
ANALGESICS/NARCOTICS	**ANTICONVULSANTS**	**LIPID-LOWERING AGENTS**
Acetaminophen†	Phenytoin*†	Fibrates
Codeine	Gabapentin	Rosuvastatin
Hydromorphone	Pregabalin	**MISCELLANEOUS**
Morphine	Topiramate	Allopurinol
Oxycodone*	**ANTIDEPRESSANTS**	Amantadine*
Tramadol*	Duloxetine	Baclofen
ANTIBIOTICS	Escitalopram	Bisphosphonates
Cefaclor	Mirtazapine	Cetirizine
Cefixime	Venlafaxine	Colchicine
Cefuroxime axetil	**ANTIVIRALS**	Digoxin
Cephalexin	Acyclovir	Febuxostat
Ciprofloxacin	Famciclovir	Fluconazole
Clarithromycin	Oseltamivir	Lithium
Co-trimoxazole	Ribavirin	Magnesium Hydroxide
Levofloxacin	Tenofovir*	Metoclopramide
Nitrofurantoin	Valacyclovir	Memantine
ANTICOAGULANTS	**ORAL HYPOGLYCEMICS**	Ranitidine
Apixaban	Canagliflozin	Sildenafil
Dabigatran	Dapaglifozin	Sotalol
Dalteparin	Gliclazide*	Spironolactone
Edoxaban*	Empagliflozin	Sucralfate*
Enoxaparin	Glyburide	Tadalafil
Rivaroxaban	Liraglutide†	Varenicline
Tinzaparin	Metformin	
ANTI-MUSCARINICS	Saxagliptin	
Solifenacin*	Sitagliptin	
Tolterodine*		

*medications added by the Delphi panel after the first round

†medications excluded by Delphi panel

Table S2. Medications recommended by Delphi Panel for dose adjustment or avoidance based on eGFR.				
	eGFR ranges (ml/min/1.73 m^2)			
Medication	**<15**	**15-29**	**30-44**	**45-59**
Analgesics/Narcotics				
Codeine				
Hydromorphone				
Morphine				
Oxycodone				
Tramadol				
Antibiotics				
Cefaclor				
Cefixime				
Cefuroxime Axetil				
Cephalexin				
Ciprofloxacin				
Clarithromycin				
Co-trimoxazole				
Levofloxacin				
Nitrofurantoin				
Anticoagulants				
Apixaban				
Dabigatran				
Dalteparin				
Edoxaban				
Enoxaparin				
Rivaroxaban				

Tinzaparin				
Anticonvulsants				
Gabapentin				
Pregabalin				
Topiramate				
Antidepressants				
Duloxetine				
Escitalopram				
Mirtazapine				
Venlafaxine				
Antimuscarinics				
Solifenacin				
Tolterodine				
Antivirals				
Acyclovir				
Famciclovir				
Oseltamivir				
Ribavirin				
Tenofovir Disoproxil				
Valacyclovir				
Oral hypoglycemics				
Canagliflozin				
Dapagliflozin				
Empagliflozin				
Gliclazide				
Glyburide				
Metformin				

Saxagliptin				
Sitagliptin				
Lipid-Lowering Agents				
Fibrates				
Rosuvastatin				
Other drugs				
Allopurinol				
Amantadine				
Baclofen				
Bisphosphonates				
Cetirizine				
Colchicine				
Digoxin				
Febuxostat				
Fluconazole				
Lithium				
Magnesium Hydroxide				
Memantine				
Metoclopramide				
Ranitidine				
Sildenafil				
Sotalol				
Spironolactone				
Sucralfate				
Tadalafil				
Varenicline				

Abbreviations: eGFR: estimated glomerular filtration rate.

Black: avoid use; Grey: dose adjust; White: no dose adjustment required.

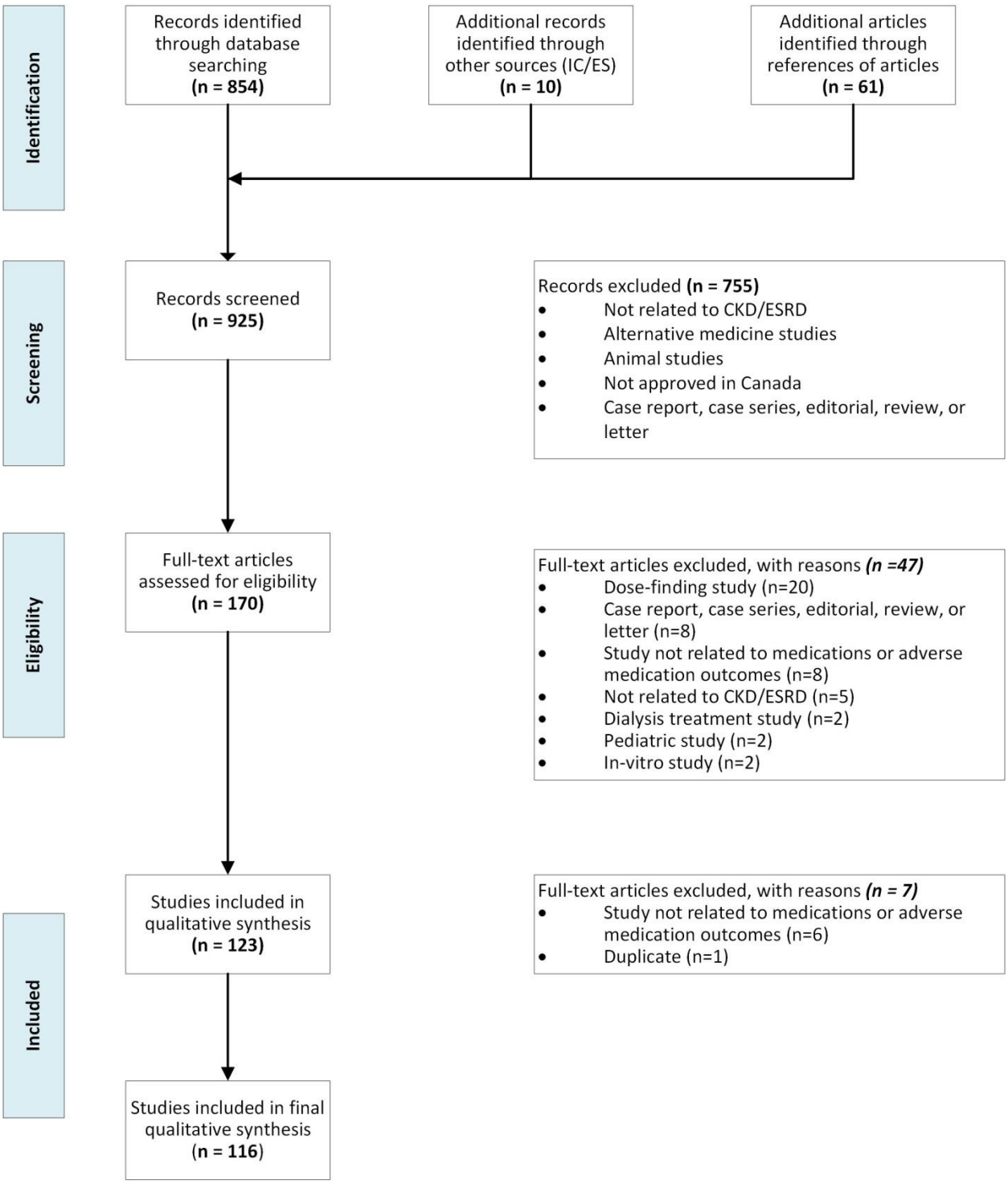

Figure S1. Flow chart of retrieved full-text articles. Abbreviation: IC/ES: Formerly known as the Institute for Clinical Evaluative Sciences.

Search strategy and terms

Date range: July 1, 2014 to present.

Language(s): English

Database(s): PubMed, Medline, Embase, International Pharmaceutical abstracts, Cochrane Database of Systematic Reviews

Search strategy:

Set 1 AND (Set 2 OR Set 2b) NOT Animals

Pubmed search

Set 1

"Drug-Related Side Effects and Adverse Reactions"[MeSH] OR "Inappropriate Prescribing"[MeSH] OR "medication errors"[MeSH] OR "Drug Dosage Calculations"[MeSH] OR "Patient Safety"[majr] OR "Abnormalities, Drug-Induced"[MeSH] OR "medication reconciliation"[MeSH] OR "Medication Systems"[MeSH] OR "Drug Prescriptions"[MeSH] OR "Pharmacokinetics"[Mesh]

OR

((medication[ti] OR drug[ti]) AND (discrepanc*[ti] OR safety[ti] OR verification*[ti] OR reconciliation[ti] OR system[ti] OR systems[ti] OR omission[ti] OR omissions[ti] OR problem[ti] OR problems[ti] OR error[ti] OR errors[ti] OR interaction[ti] OR interactions[ti] OR kinetics[ti] OR toxicity[ti]))

OR

((inappropriate*[ti]) AND (Drug[ti] OR prescribing[ti] OR prescription[ti] OR Prescribed[ti])) OR “adverse drug reactions”[ti] OR adverse drug events[ti] OR pharmacokinetics[ti]

AND

Set 2

"Renal Insufficiency, Chronic"[Mh:noexp]

chronic kidney[ti] OR chronic renal[ti] OR chronic glomerul*[ti] OR chronic nephro*[ti] OR progressive kidney[ti] OR progressive glomerul*[ti] OR progressive nephro*[ti] OR dialy*[ti] OR hemodia*[ti] OR haemodia*[ti] OR ckd[ti] OR esrd[ti]

OR

((diabet*[ti] OR "Disease Progression"[majr] OR "Recurrence"[majr]) AND nephropath*[ti])

OR

uremi*[ti] OR uraemi*[ti] OR proteinuri*[ti] OR nephrosclerosis[ti] OR glomerulosclerosis[ti] OR glomerular sclerosis[ti]

OR

((kidney[ti] OR renal[ti]) AND (ckf[ti] OR crd[ti] OR crf[ti] OR eskd[ti] OR eskf[ti] OR esrf[ti] OR end-stage[ti] OR endstage[ti] OR eGFR[ti])) OR kidney disease*[ti] OR kidney failur*[ti] OR kidney function*[ti] OR kidney insufficienc*[ti] OR kidney disorder*[ti] OR kidney dysfunction[ti]

OR

"Glomerular Filtration Rate"[majr]

OR

Set 2b

Acute Kidney Injury[Majr] OR Oliguria[Majr]

OR

(acute[ti] AND (kidney[ti] OR renal[ti])) OR (acute[ti] AND (kidney[ti] OR renal[ti] OR nephr$[ti] OR tubular[ti] OR dialys$[ti])) OR ((kidney[ti] OR renal[ti]) AND isch?emi$[ti])

(Induced[ti] AND (kidney injury[ti] or renal injury[ti]))

Oliguria[ti]

(pre-renal[ti] OR prerenal[ti]) OR ((arf[ti] OR aki[ti]) AND (renal[ti] OR kidney*[ti]))

((induced AND (kidney OR renal)) AND nephrotox*)

NOT

(allograft$[ti] OR glomerulosclerosis[ti])

(nephropath$ AND ((contrast$ AND (medi$ OR induced OR agent$)) OR radiocontrast$ OR iodinated OR crystal$ OR cast))

Kidney Tubules, Proximal[MeSH]

((((kidney[ti] OR renal[ti]) AND isch?emi$[ti]) OR ur?emi$[ti] OR (renal inflammation[ti]) AND (Reperfusion Injury[majr] OR (isch?emi$[ti] OR reperfusion[ti]) OR injury[ti] OR acute[ti]))

(((acute[ti] OR chronic[ti]) AND (kidney[ti] OR Renal[ti]) AND (injur*[ti] OR injuries[ti] OR insufficienc*[ti] OR failure*[ti] OR damage*[ti] OR disease*[ti])))

NOT

((Animals[MESH] OR Animal Experimentation[MESH] OR "Models, Animal"[MESH] OR animal*[tw] OR nonhuman[tw] OR non human[tw] or rat[tw] OR rats[tw] OR mouse[tw] OR mice[tw] OR rabbit[tw] OR rabbits[tw] OR pig[tw] OR pigs[tw] OR porcine[tw] OR swine[tw] OR dog[tw] OR dogs[tw] or hamster[tw] OR hamsters[tw] or fish[tw] or chicken[tw] OR chickens[tw] or sheep[tw]) NOT (Humans[MESH] OR human[tw]))