

Mitigating Medication Errors Post-Transplant



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Accreditation Statement



The Canadian Council on Continuing Education in Pharmacy has accredited this program for 1 CEU.

Learning Objectives

Upon completion of the program, participants will be able to:

- Recognize the volume of medications and complexity of medication regimens taken by transplant recipients
- Explain the drug-specific, patient-specific, and clinician-specific factors which increase the risk of medication errors in transplant patients
- Discuss and incorporate practice tips presented to minimize the risk of medication errors in transplant patients

Definition of medication error

"A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer."



"Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use."



Question

Medication errors affect how many patients annually (based on a recent US publication)?



- A. 1 million
- B. 3 million
- C. 5 million
- D. 7 million

Medication error is frequent and is the third leading cause of outpatient visits

Frequency (US data)



7 million
patients annually

~3.5 million
doctor visits
annually

1 million ED
visits annually

500,000
medication errors
daily

Morbidity and mortality



3rd
leading cause of
outpatient visits*

Higher rate of
mortality than traffic
accidents, auto-
immunodeficiency
syndrome, or
breast cancer

Responsible for
5–41%
of hospital
admissions

Responsible for
22%
of readmissions
after discharge

↑ risk of:

- drug–drug interactions
- frequency of hospital admissions and outpatient visits
- length of hospital stay
- management cost
- mortality

*After CV diseases and cancer.

CV, cardiovascular.

Rasool MF, et al. *Front Public Health*. 2020;8:531038.

Medication errors post-transplant are abundant in the outpatient setting



Objective

- To understand and classify causal factors linked to medication errors



Methods

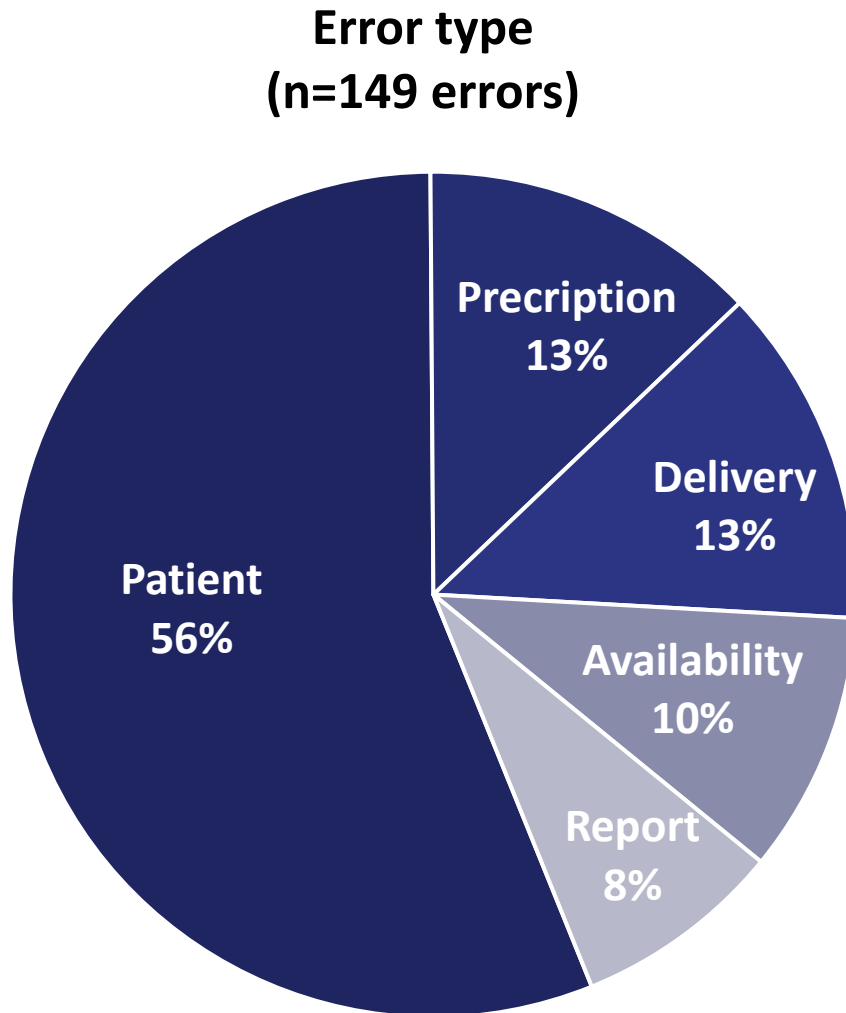
- Recipients of liver, kidney, and/or pancreas allografts (n=93 patients)
- Patients were followed up by an academic medical centre over 12 months

Results

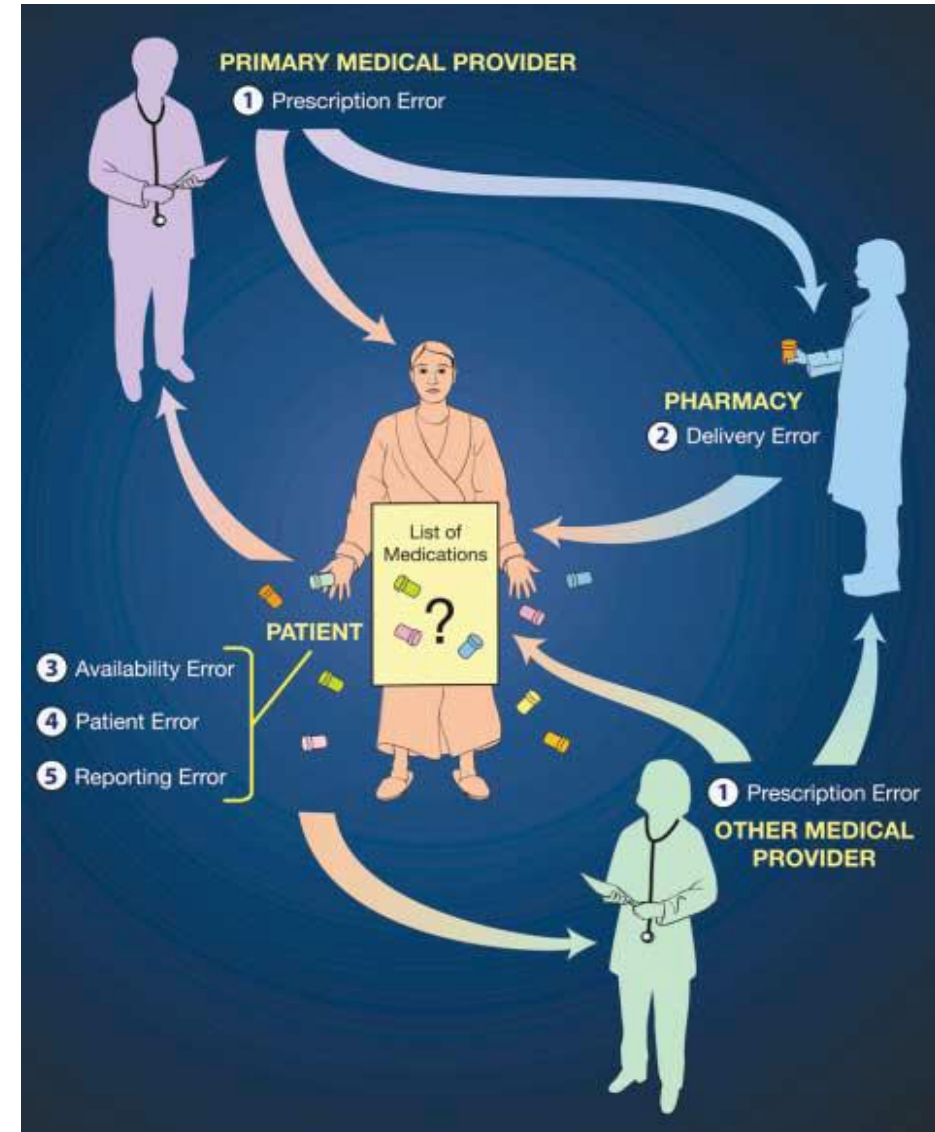


- 149 medication errors were identified
- Patients were prescribed a mean of 10.9 medications each

Different types of medication errors were identified



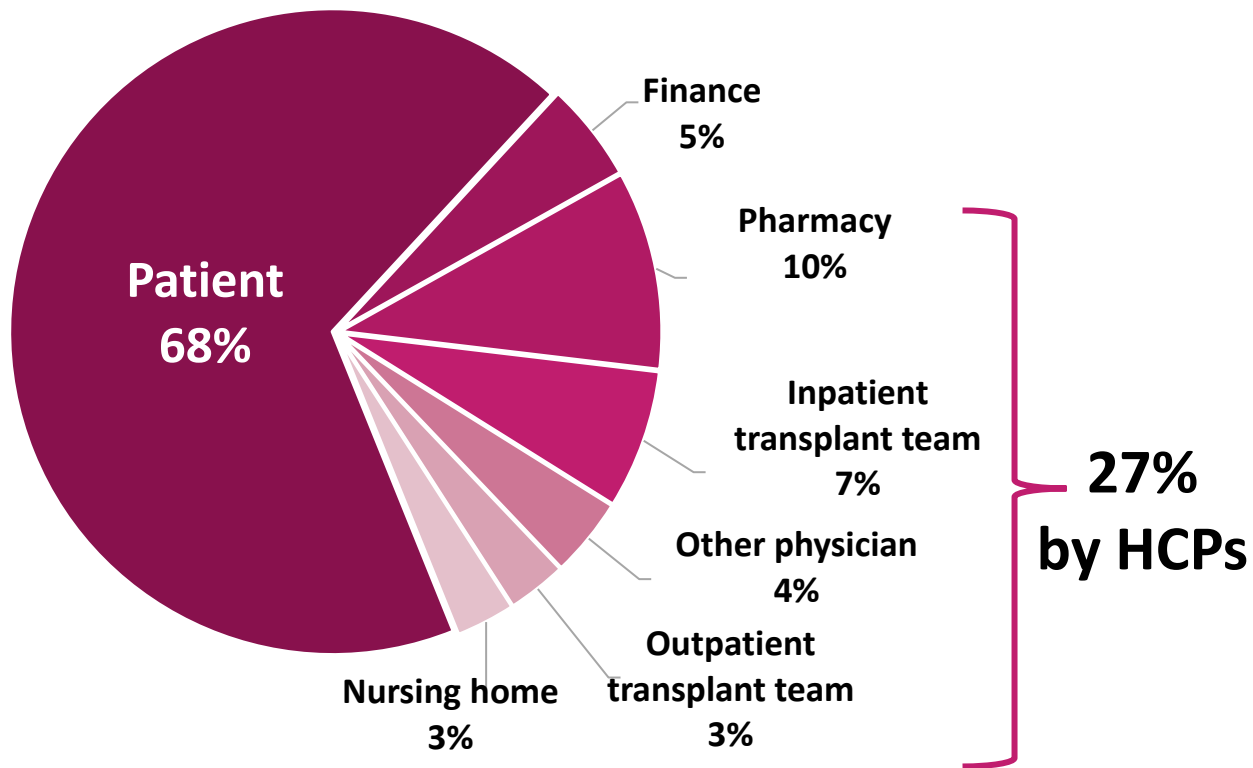
Friedman AL, et al. *Arch Surg.* 2007 Mar;142(3):278-83.



Patients and HCPs are at the root cause of most medication errors which can result in significant AEs



Root causes



Adverse events associated with 32% of the medication errors

- 17 hospitalizations
- 3 outpatient procedures
- 9 episodes of rejection
- 6 failed transplants

Medication errors and adverse drug events in kidney transplant patients

Objectives



- To determine the incidence and risk factors for MEs and ADRs
- To determine the association between transplant outcomes and these events

Methods



- Adult kidney transplant patients (n=200)
- Mean study follow-up was 2.5 ± 0.7 years

Medication error (ME):

- Documented by a nurse, physician, or pharmacist that a patient was taking a medication in an unintended manner

Clinically significant medication error (CSME):

- ME that reasonably contributed to a hospitalization

Adverse drug reaction (ADR):

- Response to a drug that is noxious and unintended, severity assigned as per standardized classification system

MEs and ADRs occur in a majority of kidney transplant recipients

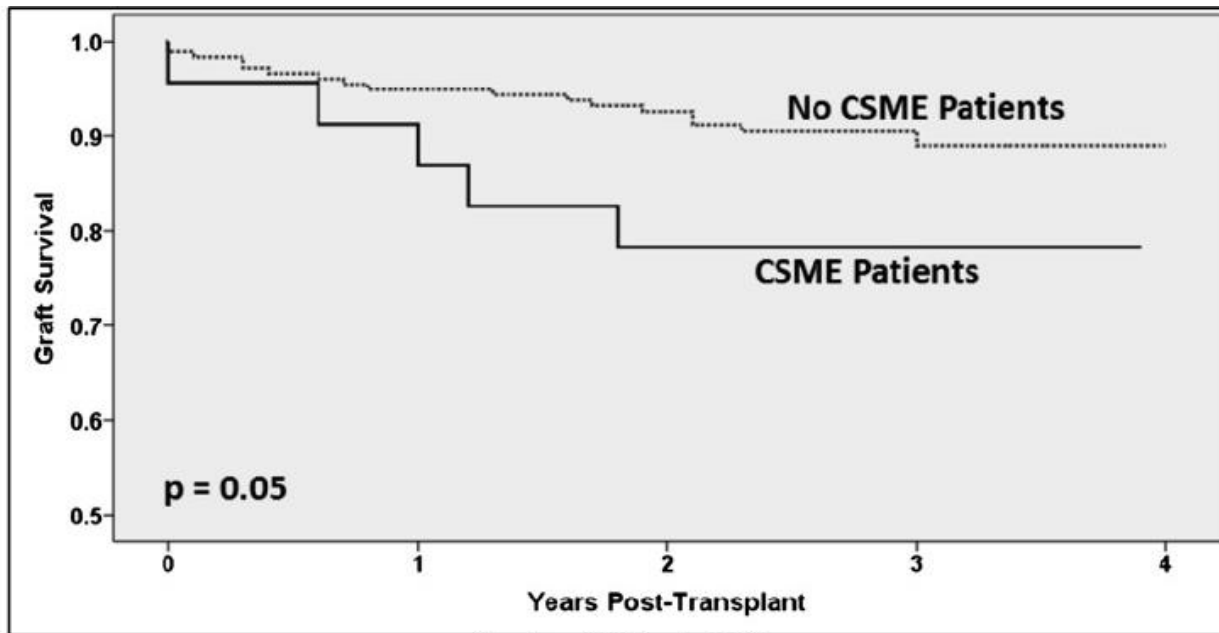
Results

- Total number of MEs identified: 233
- 64% of patients had at least 1 ME
- Usually caused by patient-related factors
 - i.e., taking the wrong dose, the wrong drug, or a medication not prescribed
- 1 in 8 patients had a significant ME that contributed to a hospitalization
- Those with CSME were more likely to have:
 - Additional MEs
 - Hospital readmissions
 - ADRs
 - Graft loss

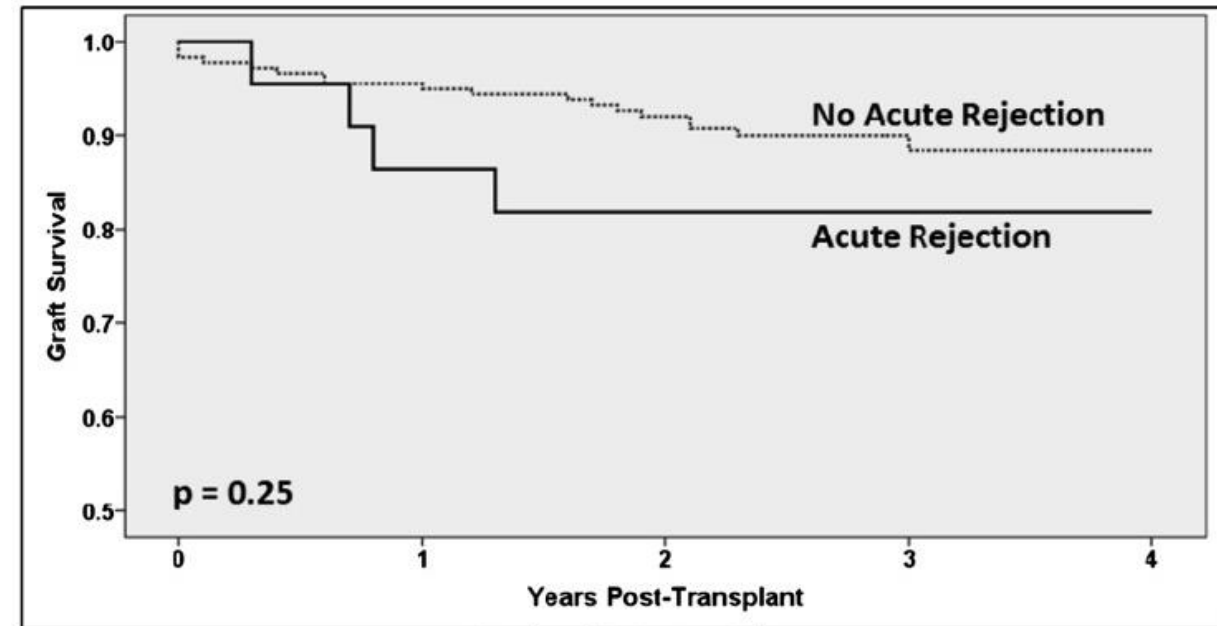
Type of ME or ADR	Frequency
ME by drug class	
Immunosuppressant	48%
Other	17%
Antihypertensive	12%
Antibiotics	10%
Not noted	7%
Diabetes mellitus	5%
NSAIDs	1%
ADRs by type	
Metabolic	42%
Cytopenia	17%
Opportunistic infection	17%
Gastrointestinal	15%
Rejection	7%
Neurologic	3%
Dermatologic	0.1%

Patients that developed a CSME were more likely to have graft failure compared with non-CSME patients

Kaplan-Meier survival curves for graft loss



Number of Patients at Risk					
Group	Year 0	Year 1	Year 2	Year 3	Year 4
No CSME	177	168	141	60	2
CSME	23	21	17	7	0



Number of Patients at Risk					
Group	Year 0	Year 1	Year 2	Year 3	Year 4
Rejection	178	170	142	59	1
No Rejection	22	19	16	8	1

Complicated procedures – interpreting drug levels



Drug level drawn

- Timing?
- Consistent recent dosing?
- Lab factors
- Drug interactions
- Documentation

Interpretation

- Accurate current dose on file?
- Communication to prescriber
- Decision regarding dose
- Documentation/transcription
- Communication to patient

Prescription

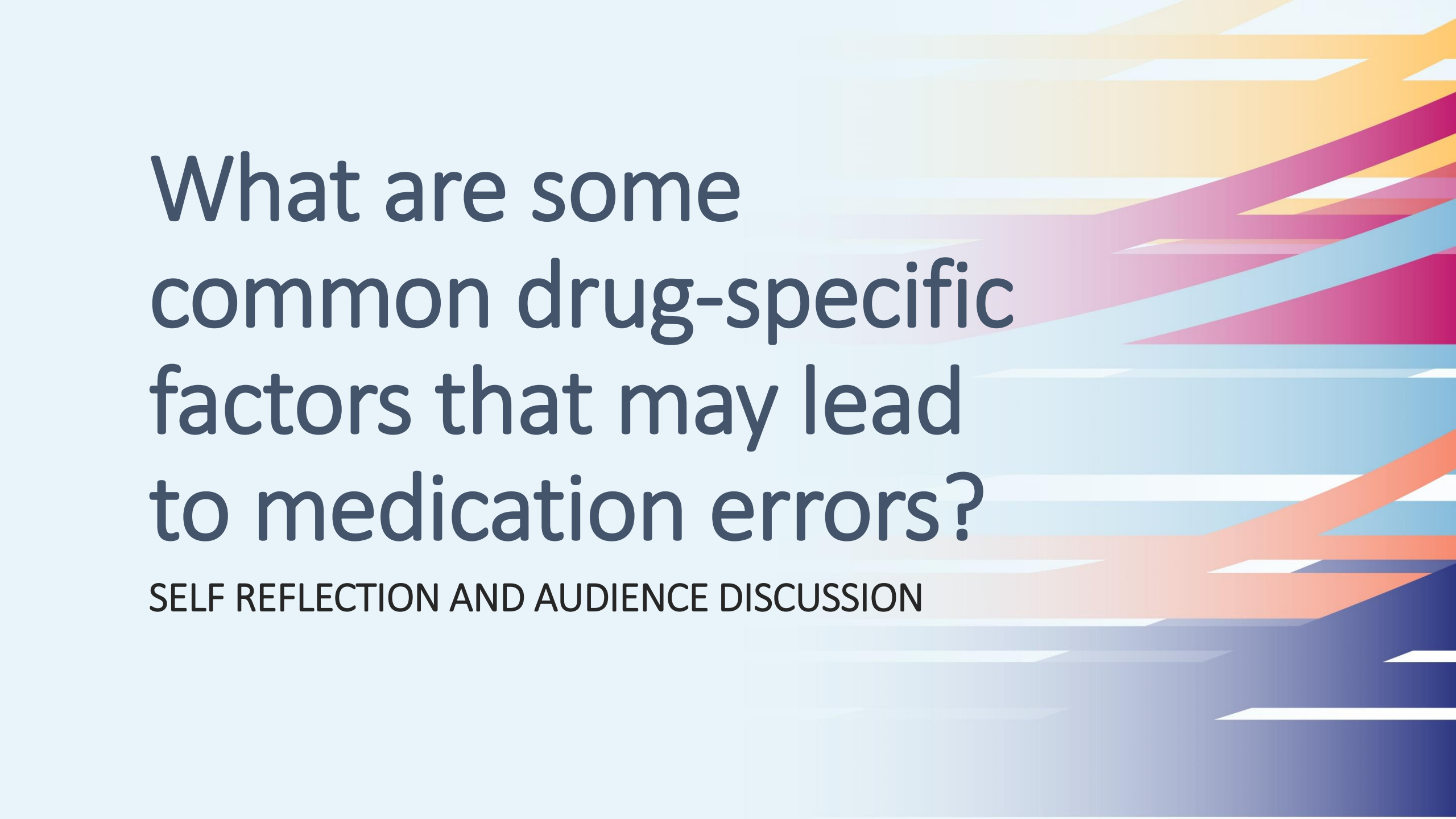
- Dose
- Formulation
- Quantity
- Pharmacy

Dispensing

- Formulation
- Dose
- Availability
- Communication to patient
- Updating adherence packaging
- Blister pack supply

Patient

- Understanding/health literacy
- Timeliness
- Dose/numeracy



What are some
common drug-specific
factors that may lead
to medication errors?

SELF REFLECTION AND AUDIENCE DISCUSSION

Polypharmacy is common in adults and more pronounced in older adults (>65 years)

Polypharmacy = using ≥ 5 concomitant medications

Canadian data

**65.5% of adults
aged 40–79
used at ≥ 1 prescription
drug in the past 30 days**

**18.8% used at
 ≥ 5 prescription drugs**

Polypharmacy is more pronounced in older adults

**44% of men and
57% of women
older than age 65 take
 ≥ 5 medications/week**

**12% of men
and women
take ≥ 10
medications/week**

Polypharmacy increases the risk of medication-related problems resulting in higher risk of morbidity/mortality

Risk of medication-related problems:



- Drug–drug interactions (azoles, non-dihydropyridine CCB, nirmatrelvir-ritonavir)



- Suboptimal therapeutic response



- ↑ risk of adverse drug events



- ↓ medication adherence



- ↑ risk of medication errors

Associated with:



- Poorer quality of life



- ↑ healthcare utilization with higher healthcare costs



- ↑ risk of morbidity and mortality

CCB, calcium channel blocker.

1. van Oosten MJM, et al. *Clin Kidney J.* 2021 Jul 6;14(12):2497-2523; 2. Mason NA, Bakus JL. *Semin Dial.* 2010;23:55-61; 3. Mason NA. *Curr Opin Nephrol Hypertens.* 2011;20:492-497; 4. Payne RA. *Clin Med (Lond).* 2016;16:465-469; 5. Battistella M, et al. *Can J Kidney Health Dis.* 2018;5:2054358118760832. 6. Park HY, et al. *Int J Clin Pharmacol Ther.* 2016;54:369-377.

Polypharmacy and medication use in patients with CKD with/without kidney replacement therapy compared to matched controls

The aim of the study was to examine polypharmacy prevalence in CKD patients

Methods



Dutch health data: Vektis

Case: control study – 1:2,
matched by age, sex and
socioeconomic status (SES)



• CKD G4/G5 without dialysis



• CKD on dialysis



• Kidney transplant



• Control: without CKD



Polypharmacy (PP):

≥ 5 drugs



Excessive PP (EPP):

≥ 10 drugs



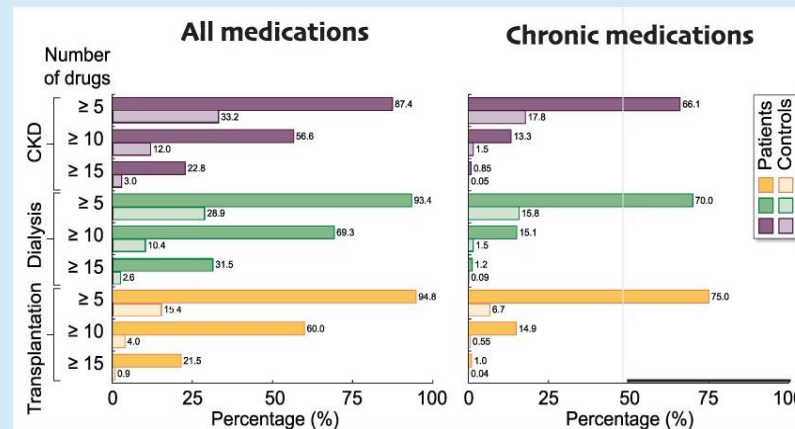
Hyperpolypharmacy (HPP):

≥ 15 drugs

Results

27 573 patients

14 905 patients with **CKD G4/G5**, mean age 75.6 years
3 872 patients on **dialysis**, mean age 70.8 years
8 796 **transplant** patients, mean age 56.5 years



Median number of dispensed meds:
CKD G4/G5 = 10; control = 1
Dialysis = 12; control = 1
Transplant = 11; control = 0

Median number of dispensed meds:
CKD G4/G5 = 6; control = 0
Dialysis = 6; control = 0
Transplant = 6; control = 0



PP, EPP, HPP higher in
patients than in controls
(ratio 2.6 to 23.9)

Risk factors:

- Age (CKD, transplant)
- Lower SES
- Diabetes
- ER visit
- Vascular disease
- Hospitalization



Common chronic drugs:

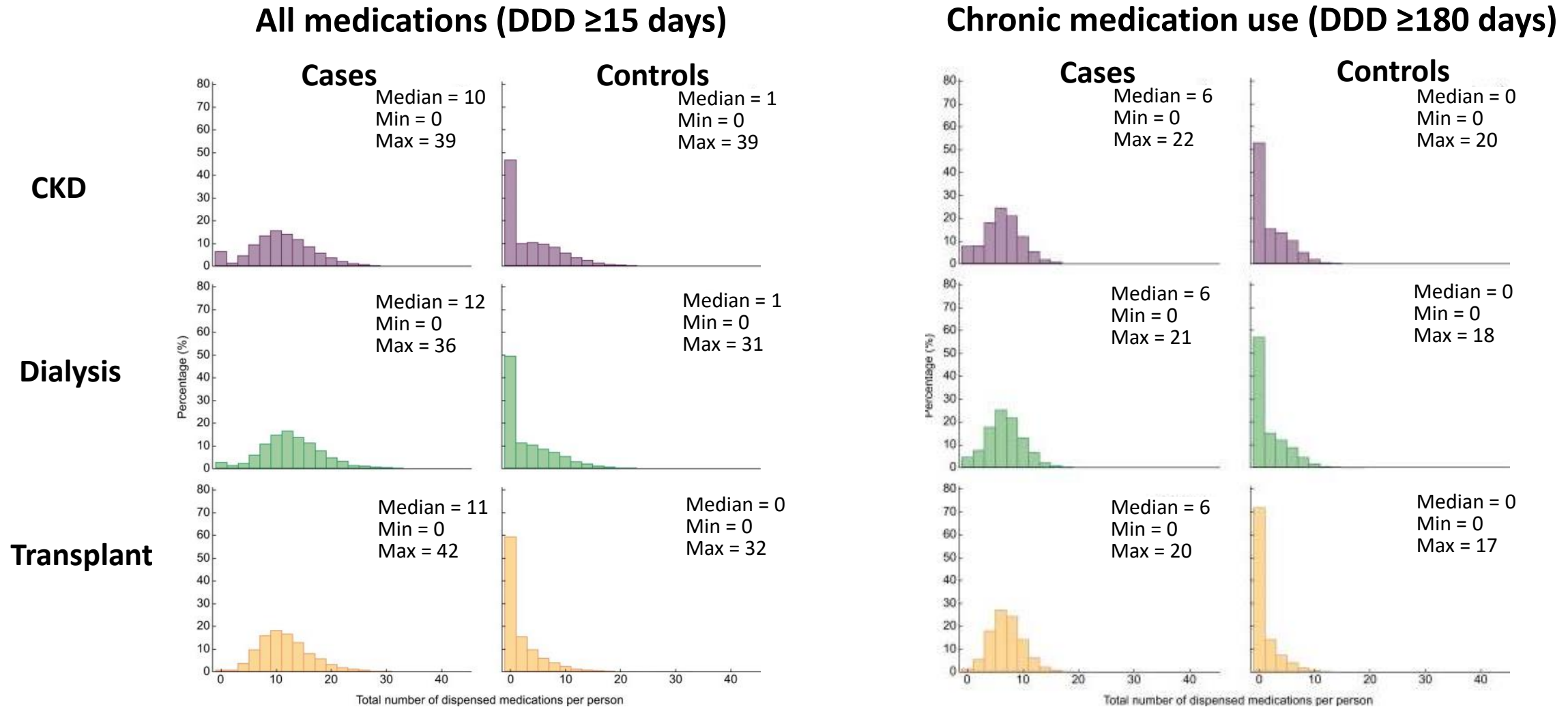
- Proton pump inhibitors
- Statins



Conclusion: CKD stage G4/G5, dialysis and kidney transplant patients had high medication burden, far beyond that of the general population. A critical approach to medication prescription could be a first steps towards a more appropriate medication use.

van Oosten MJM, et al
Clinical Kidney Journal (2021)
@CKJsocial

The median number of dispensed medications is much higher in transplant cases compared to controls



CKD, chronic kidney disease; DDD, defined daily dose.

Van Oosten MJM, et al. *Clin Kidney J.* 2021;14(42):2497-2523.

Variables associated with PP in kidney transplant patients include older age, DM, vascular disease, and ER visit

	Odds Ratio	95% CI
Age categories (years)		
20–64	Ref	-
65–74	3.69	2.89–4.71
≥75	5.88	4.60–7.51
Sex		
Female	Ref	-
Male	1.19	1.05–1.34
Socioeconomic score (categories)		
Q1	1.34	1.13–1.59
Q2	1.29	1.09–1.54
Q3	1.16	0.97–1.39
Q4	Ref	-
Diabetes mellitus^a	5.59	4.91–6.36
Vascular disease^b	2.51	2.14–2.96
Hospitalization^c	1.29	1.09–1.52
ER visit^d	1.76	1.54–2.00

Polypharmacy (PP)

- Defined as ≥5 medications for chronic medication use

^aModel adjusted for age, sex, SES, and DM.

^bModel adjusted for age, sex, SES, DM, vascular disease and ER visits.

^cModel adjusted for age, sex, SES, DM, vascular disease, hospitalization and ER visits.

^dModel adjusted for age, sex, SES, DM and vascular disease.

Question



Which of the following statements is false?

- A. Polypharmacy is associated with higher quality of life in stable kidney transplant recipients
- B. Cost-related non-adherence may lead to intentional medication errors
- C. The prevalence of potentially inappropriate drug combinations increases with the number of physicians providing medical care
- D. Poor patient numeracy skills may lead to medication errors

Polypharmacy is associated with lower QoL in stable kidney transplant recipients

Methods

- Stable kidney transplant recipients (n=136)
- Min. 12 months post-transplant
- Validated Polish Kidney Disease Quality of Life Short Form questionnaire
- Divided cohort into 3 groups based on number of medications taken

Data presented as means and 95% confidence intervals.

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; F, female; KDQOL-SF, Kidney Disease Quality of Life-Short Form; M, male; PLN, Polish currency.

*1 USD = 3.6 PLN. †Work status data were analyzed in working subjects only, n = 41.

Woźniak I, et al. *Transplantation Proceedings*. 2018; 50(6): 1896-9.

	Study Groups According to the Number of Prescribed Drugs			Statistics Turkey Test/X ² Test		
	Group 1 ≤4 (n=37)	Group 2 5-9 (n=76)	Group 3 ≥10 (n=23)	1 vs. 3	2 vs. 3	1 vs. 2
Age (y)	47 (42-51)	51 (48-54)	54 (49-58)	0.11	0.60	0.29
Sex (M/F)	19/18	42/34	13/10	0.90	0.89	0.85
BMI (kg/m ²)	25.1 (23.7-26.4)	27.1 (26.1-28.1)	29.4 (27.4-31.4)	<0.001	0.06	0.05
Retransplant (%)	10.8	7.9	13.0	0.88	0.73	0.87
Time from transplantation (y)	5.8 (4.8-6.8)	7.6 (6.5-8.8)	8.2 (6.1-10.3)	0.12	0.87	0.11
Dialysis vintage (mo)	32 (26-39)	34 (27-40)	30 (18-43)	0.96	0.87	0.97
eGFR (mL/min/1.73 m ²)	68 (62-74)	52 (47-58)	39 (33-45)	<0.001	0.02	<0.001
Hypertension (%)	37.8	77.6	87.0	<0.001	0.50	<0.001
Cardiovascular disease (%)	2.7	14.5	30.4	0.06	0.15	0.02
Diabetes (%)	5.4	25.0	26.1	0.007	0.87	0.11
Number of medications	3.2 (2.9-3.4)	6.8 (6.4-7.1)	11.6 (10.9-12.2)	<0.001	<0.001	<0.001
Total weekly pill burden	41 (36-46)	72 (128-167)	113 (103-123)	<0.001	<0.001	<0.001
Cost of medication (PLN*)	103 (77-129)	148 (128-167)	236 (197-276)	<0.001	<0.001	0.02
Dosing frequency per day	2.2 (1.9-3.4)	2.6 (2.4-2.8)	3.4 (2.8-4.0)	<0.001	0.002	0.08
Symptoms/problem list	89.0 (85.7-92.2)	86.9 (84.4-89.5)	81.8 (76.9-86.7)	0.03	0.11	0.62
Effect of CKD	87.1 (82.5-91.6)	90.3 (87.6-93.0)	81.4 (75.1-87.7)	0.22	0.01	0.43
Burden of CKD	73.5 (65.1-81.9)	82.2 (76.9-87.4)	70.9 (58.3-83.6)	0.92	0.14	0.18
Work status	95.8 (86.7-100)	94.2 (85.5-100)	66.7 (0-100)			
Cognitive function	80.2 (75.0-85.4)	83.2 (80.0-86.7)	77.1 (68.3-85.9)	0.76	0.27	0.64
Quality of social interaction	78.2 (70.9-85.5)	85.2 (81.1-89.2)	73.9 (62.8-85.0)	0.71	0.05	0.20
Sexual function	82.4 (73.7-91.1)	86.0 (80.5-91.5)	71.7 (58.1-85.4)	0.27	0.05	0.77
Sleep	75.1 (68.7-81.5)	74.4 (70.2-78.7)	69.3 (60.0-78.7)	0.49	0.51	0.98
Social support	82.9 (76.7-89.1)	82.7 (77.9-87.5)	83.3 (75.2-91.5)	0.99	0.99	0.99
Physical functioning	84.5 (77.6-91.3)	83.4 (80.2-87.1)	65.9 (54.7-77.0)	<0.001	<0.001	0.98
Role – physical	75.7 (63.8-87.5)	77.3 (69.7-84.9)	62.0 (43.2-80.6)	0.32	0.17	0.97
Pain	82.7 (75.5-89.9)	76.5 (70.6-82.5)	57.2 (45.0-69.4)	<0.001	<0.001	0.45
General health	61.4 (54.2-68.6)	58.7 (54.6-62.8)	50.2 (43.0-57.4)	0.07	0.14	0.76
Emotional well-being	75.1 (69.0-81.3)	74.8 (70.9-78.7)	69.9 (61.6-78.2)	0.51	0.49	0.99
Role-emotional	78.4 (65.5-91.3)	82.0 (74.3-89.7)	70.0 (50.2-89.0)	0.64	0.34	0.88
Social function	82.1 (75.5-88.7)	80.4 (75.3-85.5)	66.8 (54.1-79.6)	0.01	0.04	0.93
Energy/fatigue	67.7 (61.2-74.2)	65.4 (61.3-69.4)	54.8 (45.2-64.3)	0.03	<0.05	0.82

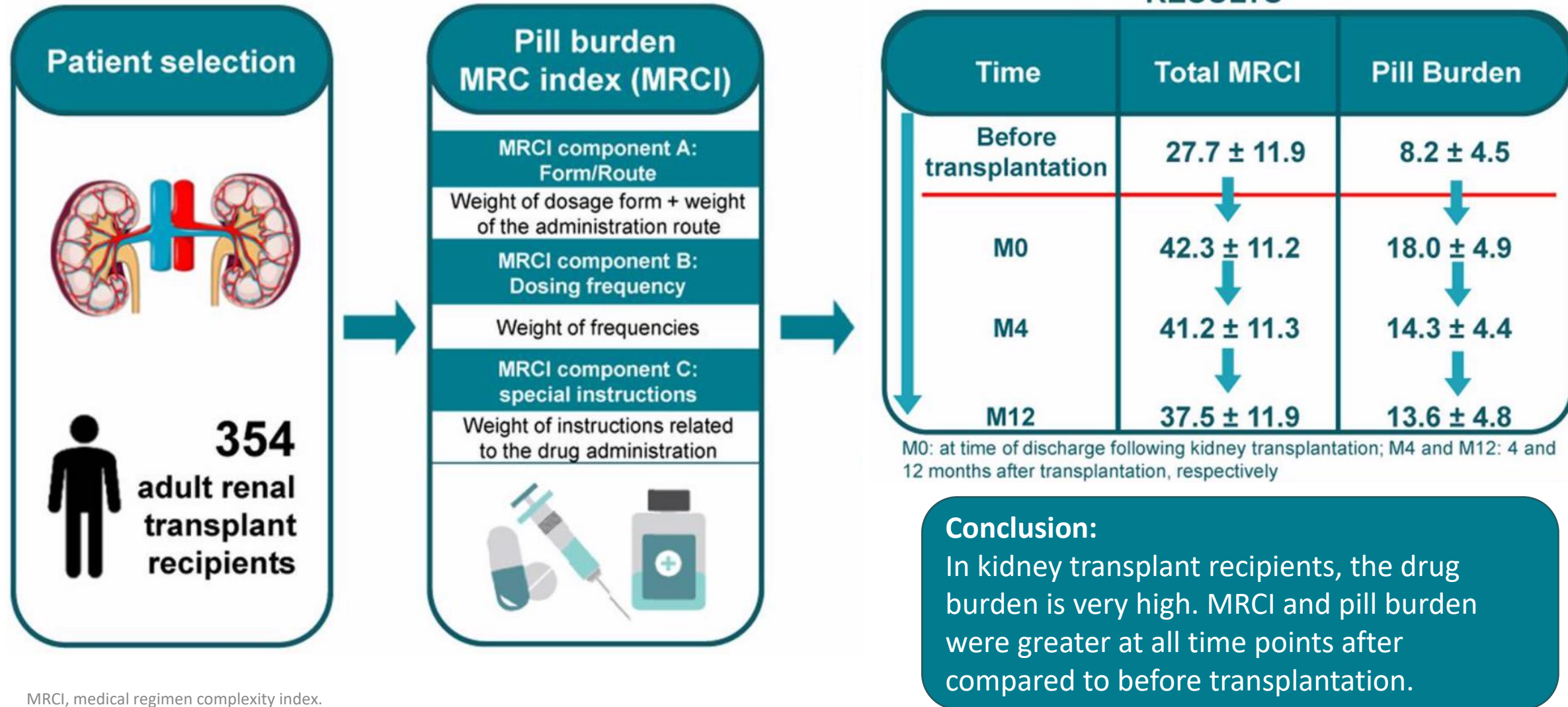
Prescribing cascades are contributors to polypharmacy, inappropriate prescribing, and medication-related harm

Drug A		Side effect		Drug B
Cardiovascular system (n=2)				
Calcium channel blocker	➡	Peripheral edema	➡	Diuretic
Diuretic	➡	Urinary incontinence	➡	Overactive bladder medication
Musculoskeletal system (n=1)				
NSAID	➡	Hypertension	➡	Antihypertensive
Urogenital system (n=2)				
Urinary anticholinergics	➡	Cognitive impairment	➡	Cholinesterase inhibitor or memantine
Alpha-1 receptor blocker	➡	Orthostatic hypotension, dizziness	➡	Vestibular sedative (e.g., betahistine, antihistamines, benzodiazepines)

Examples from transplant medications

PPI-> hypomagnesemia->magnesium supplement, mycophenolate -> gastric intolerance -> PPI -> hypomagnesemia
tacrolimus -> hypophosphatemia -> phosphate supplement -> diarrhea

Pill burden and medical regimen complexity increase after kidney transplant



Several factors correlate with medication errors, including medication from multiple prescriptions

Methods

- Japanese study of medication errors with self-administration on a Rehab unit
- n = 348; 154 patients had a total of 374 medication errors identified by nursing

	Medication error group (n=374)		No-medication error group (n=374)		Odds ratio	95% CI	P
Number of medications, median (IQR)	6	(4–8)	5	(3–7)	1.1	1.0–1.2	0.01
Number of administrations per day, median (IQR)	3	(2–4)	2	(1–3)	1.1	1.0–1.3	0.04
Dosing frequency on indicated days, n(%)	22	(6)	8	(2)	2.6	1.1–6.2	0.03
Medication from multiple prescriptions, n (%)	194	(52)	124	(33)	1.8	1.3–2.5	<0.001
Not one package or one tablet at each dosage, n (%)	287	(77)	250	(67)	0.7	0.5–1.1	0.13

Maintaining an accurate medication list may reduce the risk of medication error

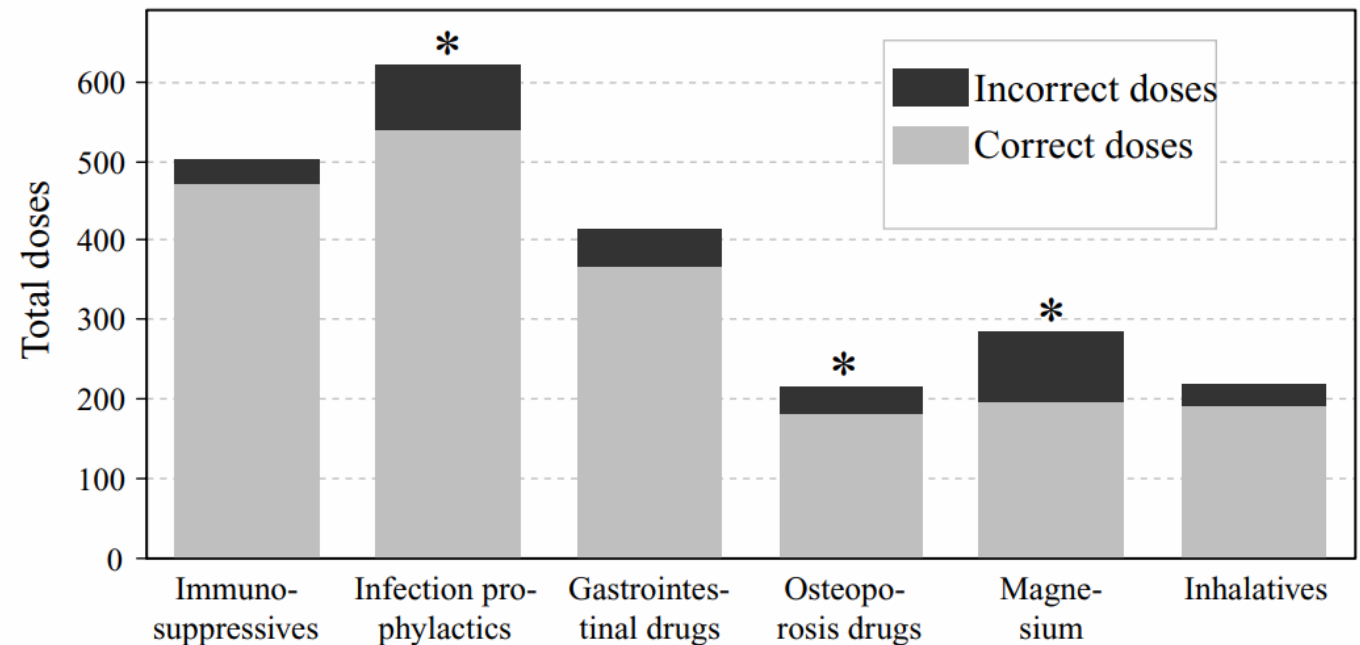
Methods

- 2006, German study
- Data collected from 101 lung transplant recipients
- Patients took a median of:
 - 15 (13–17) different drugs
 - 31 (26–38) pills daily

Results

- 13% of doses were taken incorrectly
- Lack of keeping a diary card was significantly associated with a higher rate of incorrect doses

Total number of correct and incorrect doses of different drug classes of 101 lung transplant recipients



N=101 lung transplant recipients.

*p < 0.05 chi-square of the ratio of incorrect to correct doses of other drug classes compared to immunosuppressives.

Irani S, et al. *AJT*. 2007;7(11):2561-6.

Question



Which of the following medications had the highest percentage of incidents involving anti-rejection medications according to the Institute for Safe Medication Practices (ISMP) in Canada in 2022?

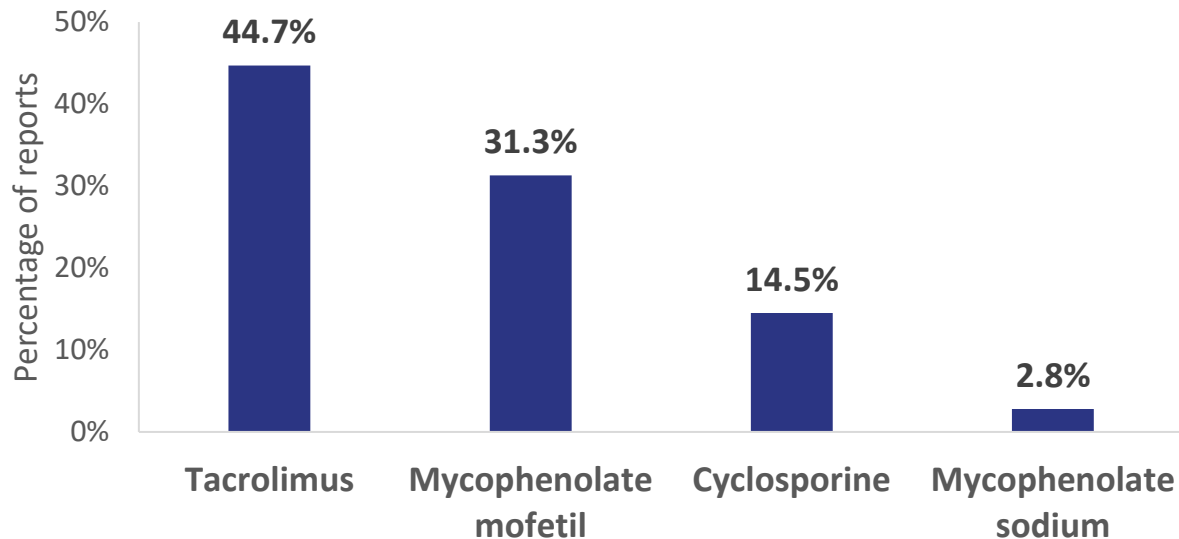
- A. Mycophenolate mofetil
- B. Tacrolimus
- C. Cyclosporine
- D. Mycophenolate sodium

ISMP Canada Safety Bulletin: Analysis of reported errors for anti-rejection medications

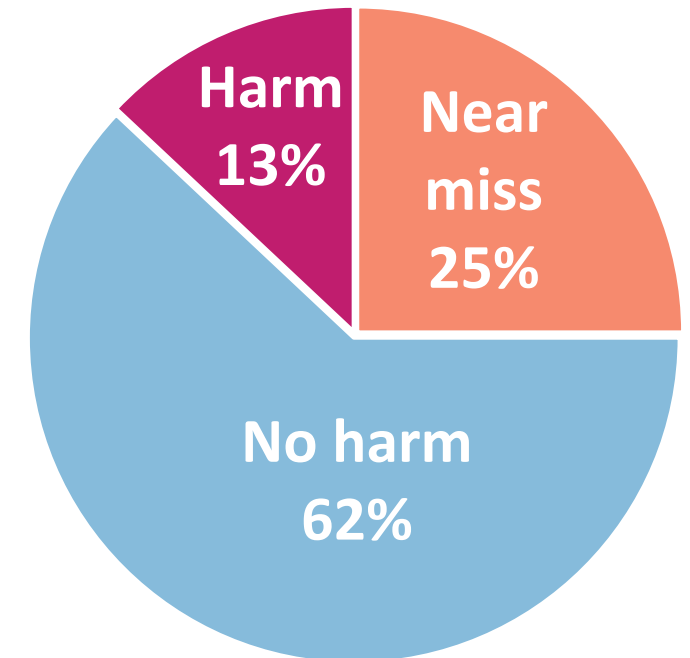
Methods

- Multi-incident analysis
- 179 incidents, 2016–2021

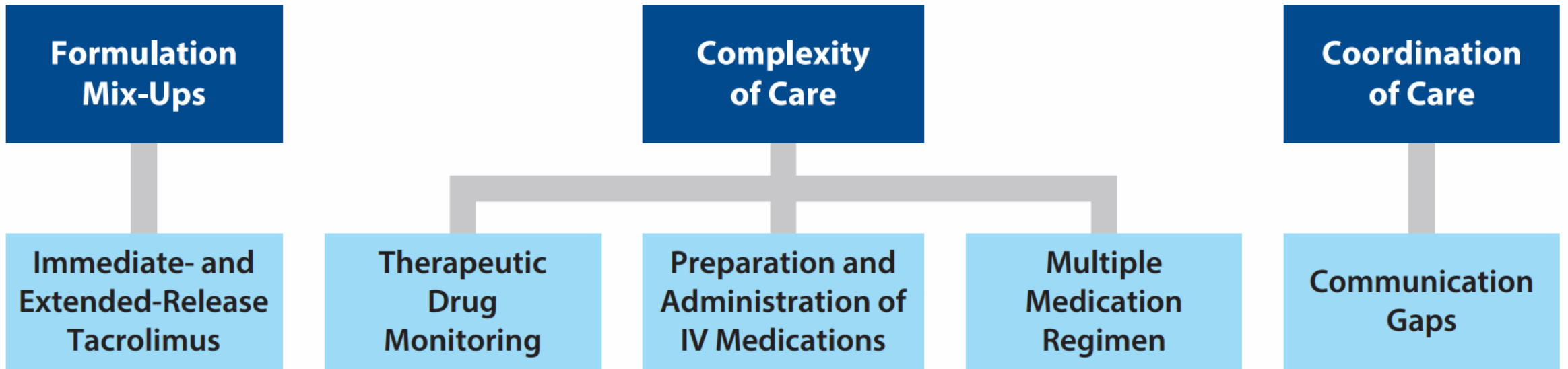
Top medications reported in incidents involving anti-rejection medications



Outcomes reported for incidence involving anti-rejection medications



ISMP identified themes and subthemes for errors associated with anti-rejection medications





ISMP, Institute for Safe Medication Practices Canada; IV, intravenous.

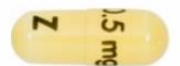
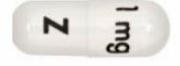

ISMP Canada Safety Bulletin Jan 19, 2022;22:1. Available at: <https://ismpcanada.ca/wp-content/uploads/2022/01/ISMPCSB2022-i1-Anti-Rejection-Medications.pdf>

Tacrolimus formulations available in Canada



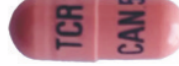
Prograf® - tacrolimus taken TWICE a day

Prograf 0.5 mg  (light yellow capsule)	Prograf 1 mg  (white capsule)	Prograf 5 mg  (pink capsule)
--------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------





Sandoz tacrolimus® – tacrolimus taken TWICE a day

Sandoz tacrolimus 0.5mg  (light yellow capsule)	Sandoz tacrolimus 1 mg  (white capsule)	Sandoz tacrolimus 5 mg  (pink capsule)
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PrACH-tacrolimus – tacrolimus taken TWICE a day

PrACH-tacrolimus 0.5 mg  (light yellow capsule)	PrACH-tacrolimus 1 mg  (white capsule)	PrACH-tacrolimus 5 mg  (pink capsule)
-------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------

Advagraf® – LONG ACTING tacrolimus taken ONCE a day

Advagraf 0.5 mg  (orange- light yellow capsule)	Advagraf 1 mg  (orange- white capsule)	Advagraf 3 mg  (orange- orange capsule)	Advagraf 5 mg  (orange- pink capsule)
-----------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------

Envarsus PA® - LONG ACTING tacrolimus taken ONCE a day

Envarsus PA 0.75 mg  (white tablet)	Envarsus PA 1 mg  (white tablet)	Envarsus PA 4 mg  (white tablet)
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Note: Generic Advagraf® (PrSandoz Tacrolimus XR) approved but not yet marketed in Canada.

BC Transplant. Tacrolimus Patients Information. Available at: http://www.transplant.bc.ca/Documents/Medications/Anti%20rejection/Tacrolimus_EN.pdf;
<https://accordhealth.ca/wp-content/uploads/2023/03/ACH-Tacrolimus-EN.pdf>

Question



Which of the following statements regarding medications errors described with tacrolimus is false?

- A. Compounding 10-fold error (e.g. 0.5 mg vs. 5 mg)
- B. Formulation mix-up (e.g. extended- and regular-release)
- C. Monitoring C2 (as opposed to C0) vs. trough levels
- D. Requiring multiple strengths to provide desired dose (e.g. patient confusion, not all strengths stocked and dispensed at the same time)

Common types and causes of medication errors with tacrolimus



Factor of 10 errors
10-fold error
(e.g., 0.5 mg vs. 5.0 mg)

Confused medication names
Tacrolimus and tamsulosin
Prograf® and Proscar®



Compounding errors
Suspension,
IV preparations



Confusion when dispensing more than 1 strength
May not all be stocked by the pharmacy and
dispensed at the same time
Patient confusion



Formulation mix-up
Extended- and
regular-release formulations



Poor communication
To patient/family or
community pharmacy
regarding dose changes



**Patients not monitored
frequently enough**
To ensure optimal trough levels



Tacrolimus and the risk of graft rejection due to medication errors: Inadvertent switching between different oral formulations

- Graft rejection and other adverse reactions from either **under- or over-exposure** to tacrolimus have been reported when patients received the wrong formulation of oral tacrolimus.
- The 3 different oral tacrolimus formulations available in Canada are **not interchangeable**. Inadvertent switching between formulations without appropriate dosing adjustments and monitoring could lead to graft rejection and other adverse reactions.
- If a prescriber intends to switch between formulations, **careful medical supervision and therapeutic monitoring are required**. Dose adjustments may be necessary to maintain blood levels in the therapeutic range.



Health Canada

Health professional risk communication (2/2)

In order to prevent inadvertent switching between tacrolimus formulations, healthcare professionals are advised to:

- Add prominent descriptors for the different formulations (e.g., '**IMMEDIATE-release**', '**EXTENDED-release**', or '**PROLONGED-release**') when identifying tacrolimus products, including on written orders, on the drug selection screens of prescribing and dispensing information systems, and in storage locations.
- Use **brand/product names** throughout the medication use process to confirm which specific formulation is intended for the patient.
- **Consider an automated alert** for computerized prescriber and pharmacy order entry that includes a warning that these formulations are not interchangeable, as well as a dosing frequency reminder.
- **Fully explain the medication** and the **different formulations** to patients and/or their caregivers and encourage them to talk to their healthcare professional if they notice a change in their medication.

Cyclosporine formulations available in Canada

Cyclosporine 10 mg, 25 mg, 50 mg, 100 mg capsules



Cyclosporine oral solution 100 mg/mL



^{PR}Sandoz Cyclosporine (Generic) 10 mg, 25 mg, 50 mg, 100 mg capsules



Medication errors described with cyclosporine



**Neoral® not interchangeable
with Sandimmune®**
Rx needs to specify
formulation to be dispensed



Sandimmune® (cyclosporine capsules and oral solution) is a **nonmodified form** of the drug that has **decreased bioavailability compared with Neoral® or Gengraf®** (cyclosporine [MODIFIED] capsules and oral solution).
Therefore, they are not interchangeable.



Monitoring:
C2 (as opposed to C0)
vs. trough levels



Liquid measurements







Dose/availability



**In some provinces (e.g., Ontario),
covered through a Special Drug
Program and dispensed through a few
designated pharmacies**
Potential for duplication
Significant risk for drug interactions

Mycophenolate formulations in Canada

Mycophenolate mofetil 250 mg  Blue and orange capsule	Mycophenolate sodium 180 mg  Light green round tablet
Mycophenolate mofetil 500 mg  Purple tablet	Mycophenolate sodium 360 mg  Light pink oval tablet

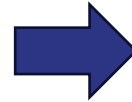
Medication errors described with mycophenolate

Acronym Confusion

MMF = mycophenolate mofetil (Cellcept®)
MPA = mycophenolic acid/mycophenolate sodium (Myfortic®)



These are not interchangeable.



Dose conversion/interpretation

720 mg MPA = 1000 mg MMF

Generics of MPA

Usually referred to as mycophenolic acid

Mycophenolate mofetil is a prodrug of **mycophenolic acid** that after oral administration is rapidly hydrolyzed to mycophenolic acid.

Mycophenolate sodium and **mycophenolic acid** are used interchangeably.

MMF, mycophenolate mofetil; MPA, mycophenolic acid/mycophenolate sodium.

1. Sanchez-Lazaro IJ, et al. Transplant Proc. 2010; 42(8):3041-3; 2. Mycophenolic Acid Available at: <https://www.sciencedirect.com/topics/immunology-and-microbiology/mycophenolic-acid> Accessed Nov 2023; 3. Expert opinion of the Steering Committee.

Reducing drug-specific medication errors



- ☐ Review medication list
 - Deprescribe unnecessary medications



- ☐ Simplify medication regimen complexity
 - Reduce overall number of dosing times per day
 - Consider drug-drug interactions and considerations around food
 - Minimize frequency (e.g., daily vs. tid)
 - Minimize pill burden (e.g., available strengths, consider combination products)



- ☐ Be specific regarding desired formulation, include description and brand name (i.e., “Tacrolimus extended-release (Advagraf)”)

0.X



- ☐ Always include a leading zero before a decimal (i.e., 0.5 mg)
- ☐ Provide patient education at transplant discharge re: dose, strengths, and how to make dose adjustments when requested
 - Ensure access to medications (cost, availability)

What are some patient-specific factors that may lead to medication errors?

SELF REFLECTION AND AUDIENCE DISCUSSION

Patient characteristics associated with medication errors in chronic disease patients

Variables	OR	95% CI	P-value
Gender, male	0.72	0.52–1.21	0.7
Age ≥60 years ★	1.9	1.3–3.1	0.001
Number of prescribed drugs ≥5	1.74	1.02–2.64	0.000
Overburden	2.2	1.64–3.56	0.000
Comorbidities ★	2.6	1.72–3.6	0.003
CCI score ★	1.31	0.49–1.84	0.004
Multiple prescribers to 1 patient	1.12	0.64–1.76	0.001
Trainee practitioner	1.03	0.61–1.65	0.003
Prescription by a specialist	0.27	0.03–0.47	0.4
Presence of previous medical record	0.63	0.17–1.39	0.09
Use of online software in prescription generation	0.69	0.23–1.39	0.1
Review of prescription by a clinical pharmacist	0.28	0.03–0.59	0.7

- ↑ age = ↑ # of medications
– ↑ vision, hearing, and dexterity issues
- ↑ comorbidities = ↑ # of medications

Low health literacy is associated with premature mortality



Health literacy: “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions”

Patient health literacy abilities

- ☐ Identification of a health issue
- ☐ To access and navigate the health system
- ☐ Communication within the health system
- ☐ Ability to co-manage the resolution of a health issue
- ☐ Language barrier

Older adults

- Low health literacy related to medicines utilization is a predictor of premature mortality
- This is independent of cognition, comorbidities, education, and socioeconomic status

Australian rheumatology study of health literacy and numeracy

Overview

- Rheumatology patients at rural and urban rheumatology clinics (n=223)
- Participants were asked to answer these questions of prescribing instructions for 5 commonly used rheumatology medications
- ~15% of rural and urban patients had low health literacy
- No difference in functional health literacy between rural and urban

Question	Answer	Pooled % incorrect
1. Tramadol is a strong pain killer. These are 50 mg tablets of tramadol. How many tablets would you need to make a dose of 150 mg?	3	4%
2. Ibuprofen is a common anti-inflammatory medication. It is called a non-steroidal anti-inflammatory or NSAID. A common adverse effect is indigestion. It therefore needs to be taken just after a meal. Ibuprofen comes in 200 mg tablets. A common dose is 400 mg twice per day. How many tablets of ibuprofen per day is that?	4	32%
3. Prednisone is a strong anti-inflammatory. These are 5 mg tablets of prednisone. Take 2 tablets once a day for 7 days. Please count out how many tablets you would need for 7 days.	14	6%

Note: Only 3 questions shown here as examples.

NSAID, non-steroidal anti-inflammatory drug.

Wong P, et al. *Medicine (Baltimore)*. 2014 Nov;93(25):e129.

Poor numeracy skills may lead to medication errors



Numeracy: Use arithmetic operations in daily tasks

- Calculating doses (number of tablets, volume of liquids, enough tablets remaining)

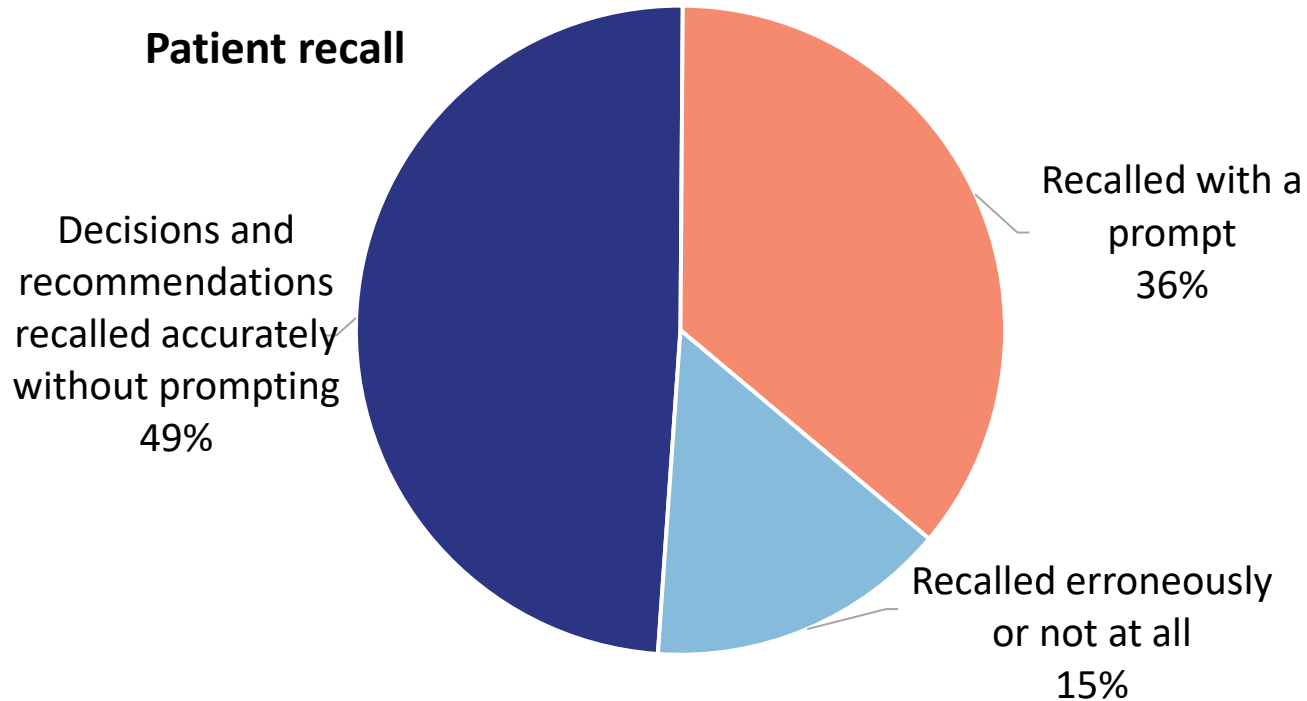
Parents' numeracy skills

- Parents with math skills $\leq 3^{\text{rd}}$ grade were 5x more likely to measure the wrong dose of medication for their child than those with skills at $\geq 6^{\text{th}}$ grade
- A third of the parents had low reading skills, 83% had poor “numeracy” skills, with 27% having skills $\leq 3^{\text{rd}}$ grade level
- Errors in tasks requiring dose measurement or measurement conversions

Poor patient recall associated with education level, # of items, and physician interaction

Methods

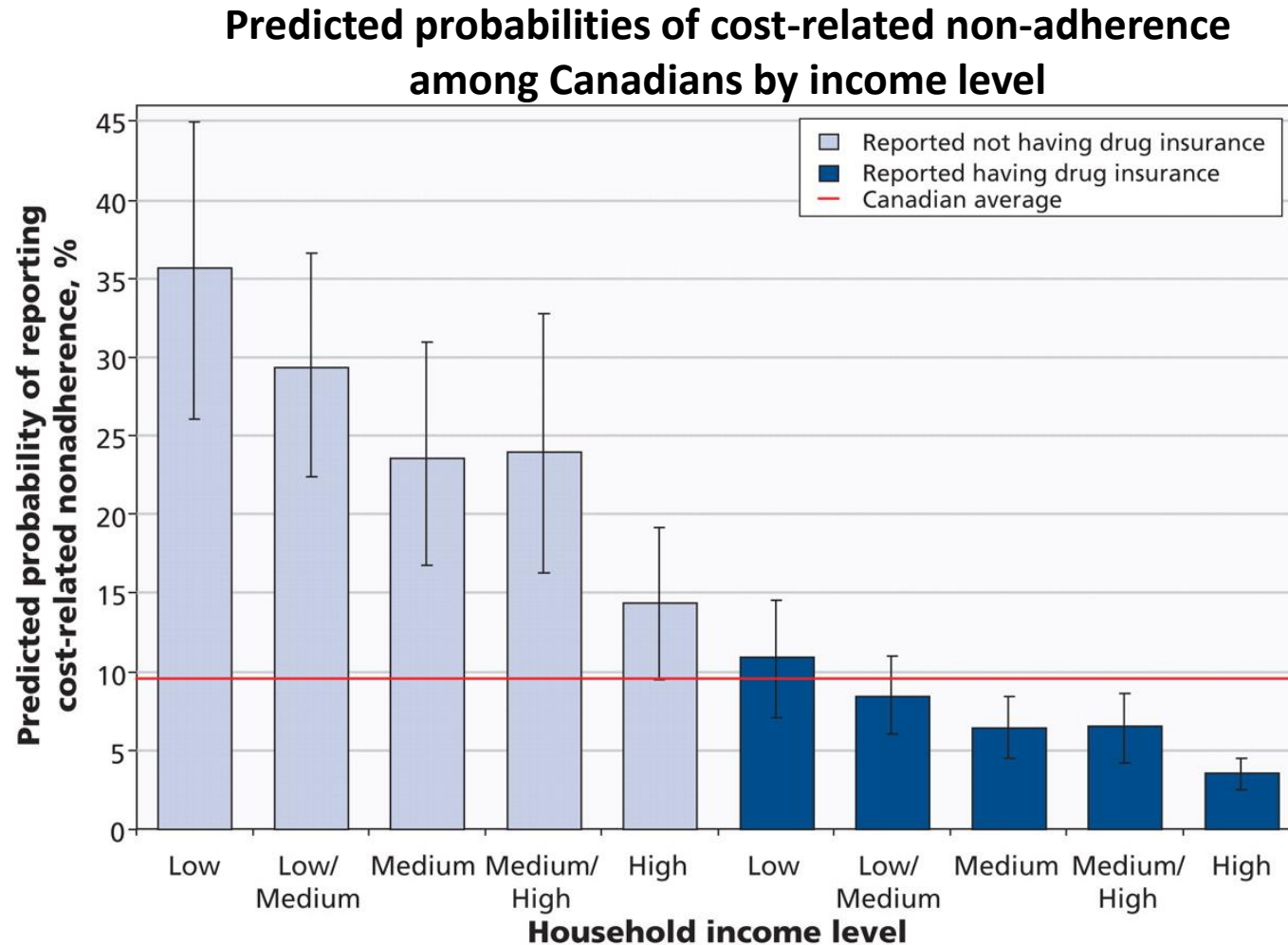
- 189 outpatient encounters in specialty ambulatory care clinics (nephrology and cardiology)
- Observational study: Recorded visits, interviewed the patient 1 week later



Poor recall associated with:

- Lower education level
- Total # of items to be recalled per visit
- Higher ratio of provider to patient talk in resolution processes (“verbal dominance”)

Financial considerations have a significant impact on adherence and intentional medication errors




Cost-related non-adherence may lead to intentional medication errors

Error bars indicate 95% confidence intervals. Income levels are based on annual household incomes: Low = less than \$20,000, low/medium = \$20,000–\$39,999, medium = \$40,000–\$59,999, medium/high = \$60,000–\$79,999, high = \$80,000 or more.
Michael R. Law et al. *CMAJ*. 2012;184:297-302.

Reducing patient-specific medication errors



- ☐ Effective patient–provider communication
- ☐ Do the math – explain how much/how many to take
- ☐ When making medication changes:
 - Review and provide patient with a written summary of medication changes
 - Update the pharmacy with a new prescription to reflect changes
- ☐ Patient – education to improve health literacy
 - Maintain a current and accurate medication list
 - Encourage adherence packaging
- ☐ Inquire if medication costs are a barrier for adherence

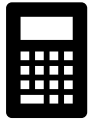


What are key clinician-specific factors that may lead to medication errors?

SELF REFLECTION AND AUDIENCE DISCUSSION

Prescribing medication errors

Numeracy errors



- Calculation errors – pediatric doses (e.g., mg/kg)
- Quantity errors (e.g., amount to prescribe for specified duration; short duration implies not needed long-term)
- Missed decimals (e.g., 0.25 vs. 0.025 mg)

Legibility errors



- Sound-alike/look-alike (e.g., Lasix® and Losec®)
- Illegible prescriptions
- Misunderstood symbols, abbreviations, or improper translation

Communication errors



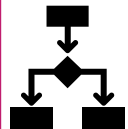
- Failure to communicate drug orders
- Inaccurate patient information (or unavailable)
- Transcription errors

Monitoring



- Failure to obtain allergy history, consider liver or renal function, or potential for drug interaction

Wrong selection errors



- Wrong patient, dose, route, or frequency
 - Knowledge gaps in formulations or salts
- Wrong drug selected from a drop-down menu

Clinician factors associated with medication errors in chronic disease patients

Variables	OR	95% CI	P-value
Gender, male	0.72	0.52–1.21	0.7
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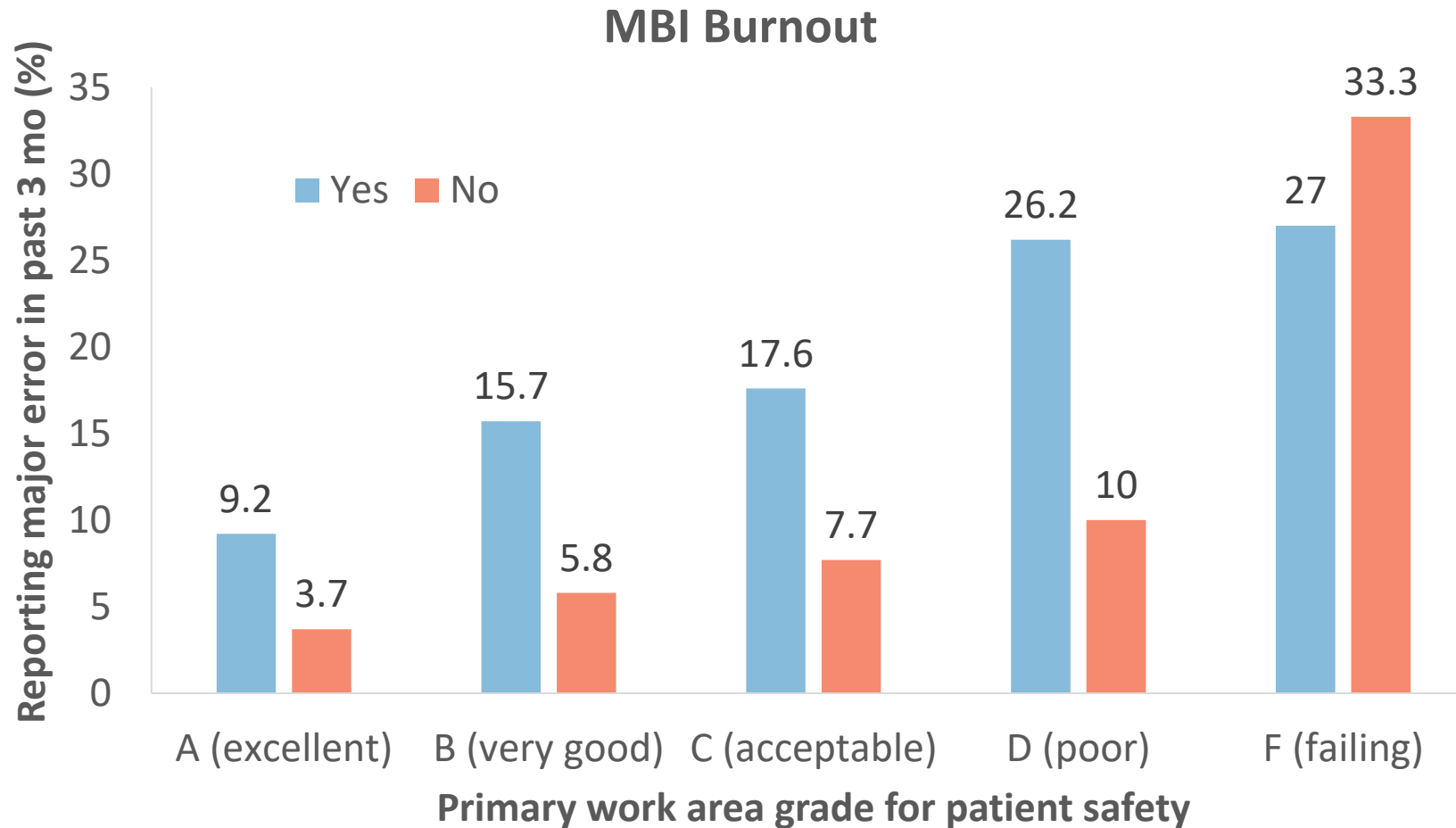
Increased risk:

- Multiple prescribers
- Trainee practitioner

Decreased risk:

- Prescription by a specialist
- Presence of previous medical record
- Online software used to generate prescriptions
- Review by clinical pharmacist

Burnout among clinicians is associated with medical errors



Reasons for errors

- Distractions
- Burnout
- Fatigue
- Suicidal ideation
- Worse unit safety grades

Work unit safety grade and prevalence or perceived major medical error, stratified by respondent burnout status.

MBI, Maslach Burnout Inventory.

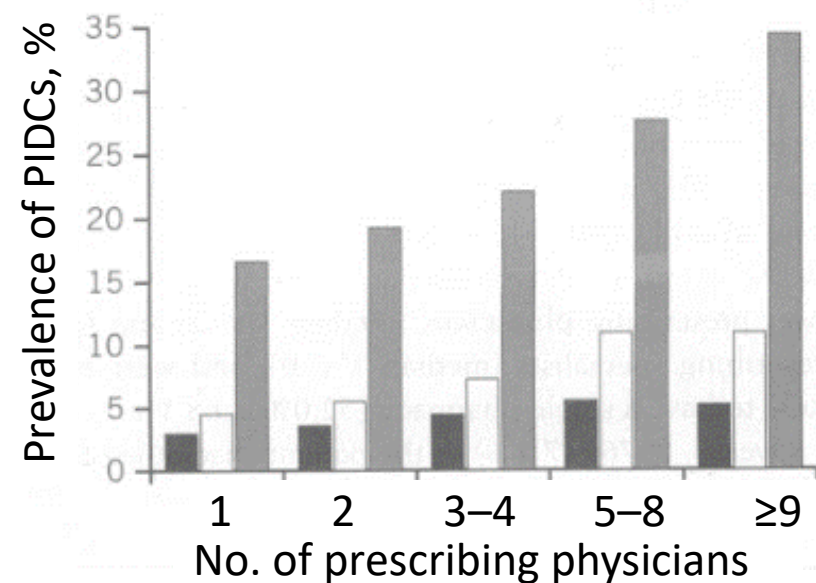
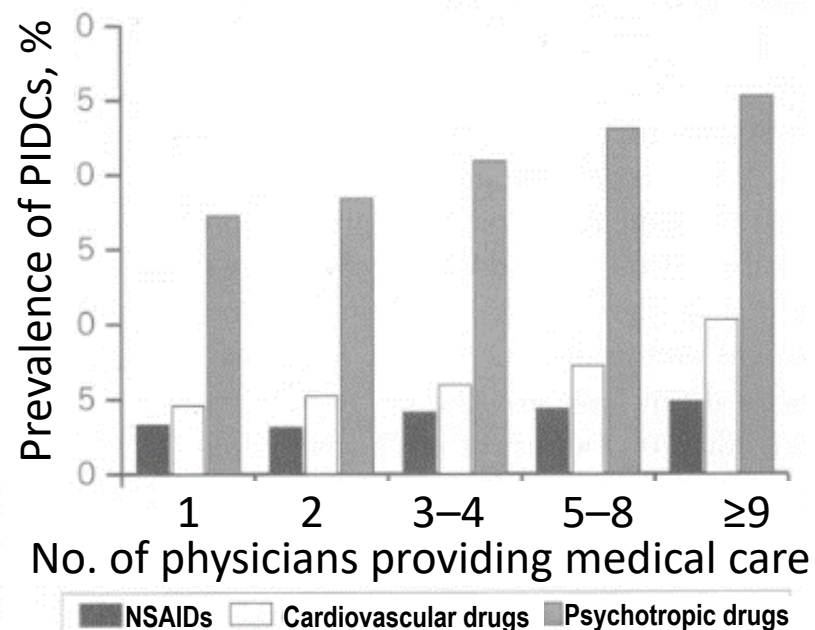
Tawfik DS, et al. *Mayo Clin Proc.* 2018 Nov;93(11):1571-1580; Expert opinion of the Steering Committee.

Multiple physician involvement in medical management leads to potentially inappropriate drug combinations (1/2)

Methods

- n > 50,000 Quebec seniors in 1990 who had visited a physician or had a Rx dispensed in 1990
- Excluded if they resided in a healthcare institution for all of 1990
- Included if they had been dispensed a cardiovascular drug, a psychotropic drug, or an NSAID

Prevalence of potentially inappropriate drug combinations



Multiple physician involvement in medical management leads to potentially inappropriate drug combinations (2/2)

Reasons for errors

- Multiple records, medication lists outdated
- Medication reconciliation not done
- Relevant prescribers not informed

Proportion of patients with a single primary care physician or a single dispensing pharmacy who had a PIDC, by type of drug combination

	Type of drug combination; % of patients with a PIDC		
Variable	Cardiovascular	Psychotropic	NSAID
Single primary care physician			
Yes	5.1	18.3	3.8
No	7.1	22.1	4.0
Odds ratio	0.70*	0.79*	0.94
Single dispensing pharmacy			
Yes	5.0	18.7	3.5
No	7.2	22.4	4.6
Odds ratio	0.68*	0.79*	0.75*

* $p < 0.001$

NSAID, non-steroidal anti-inflammatory drugs; PIDC, potentially inappropriate drug combination; Rx, prescription.

Tamblyn R, et al. *Can Med Assoc J*. 1996;154(8):1177-84.

Question



What percentage of medication errors are thought to occur due to inadequate reconciliation at admission, transfer, and discharge of a patient?

- A. <10%
- B. <20%
- C. >30%
- D. >40%

Medication reconciliation is an important step at transitions of care – inpatient issues



ISMP: “Medication reconciliation is a formal process in which healthcare providers work together with patients, families, and care providers to ensure accurate and comprehensive medication information is communicated consistently across transitions of care. Medication reconciliation requires a systematic and comprehensive review of all the medications a patient is taking (known as a BPMH) to ensure that medications being added, changed, or discontinued are carefully evaluated.”

40% of medication errors thought to occur due to inadequate reconciliation at admission, transfer, and discharge

BPMH, best possible medication history; ISMP, Institute for Safe Medication Practices.

ISMP: <https://www.ismp-canada.org/medrec/>; Barnsteiner JH. Medication Reconciliation. In: Hughes RG, editor. *Patient Safety and Quality: An Evidence-Based Handbook for Nurses*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 Apr. Chapter 38.

Available from: <https://www.ncbi.nlm.nih.gov/books/NBK2648/>

Medication reconciliation is improved with a dedicated pharmacist – outpatient issues

Overview

- Kidney transplant patients (n=200)
- Pharmacist intervention to improve accuracy of outpatient medication lists compared to that performed by transplant clinic nurses and physicians
- **Phase 1** – Baseline medication error rates
- **Phase 2** – Intervention (dedicated pharmacist)

Results

- A dedicated pharmacist significantly reduced the risk of medication discrepancies

Medication discrepancy outcomes

	Phase 1 (n=100)	Phase 2 (n=100)
Inadequate medication Reconciliation, n (%)	95 (95%)	28 (28%)
Total discrepancies (n)	398	49
Discrepancies (n)		
Average per patient	4	0.5
Minimum per patient	0	0
Maximum per patient	16	5
High-risk discrepancies (n)		
Total	73	3
Average per patient	0.75	0.03
Minimum per patient	0	0
Maximum per patient	4	1

Reduction in medication errors at discharge in transplant with a multidisciplinary approach

Methods

- N = 389, adult abdominal transplant recipients
- Retrospective analysis of a multidisciplinary project targeting an efficient, effective discharge workflow

Results

- 723 errors found over 15 months
- Median: 1.8 errors/patient
- 96% identified prior to dispensing
- Improved multidisciplinary communication and the discharge medication review process
 - Transplant pharmacist review prior to specialty pharmacy dispensing
 - Nurse review after medication delivery

Figure 1: Types of Errors

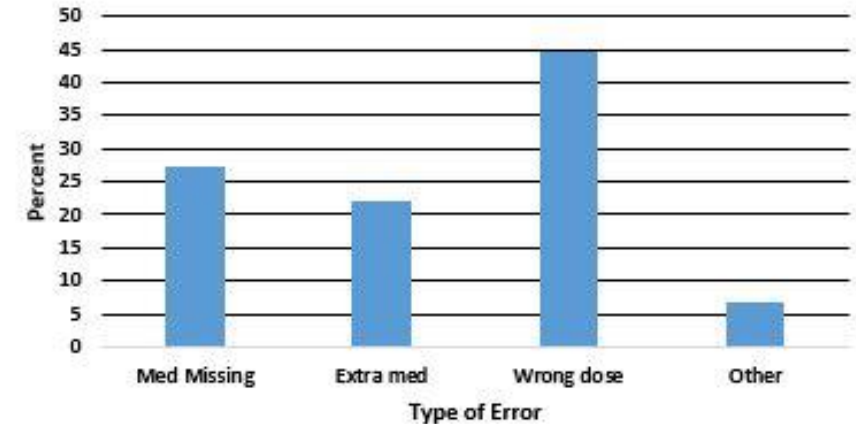
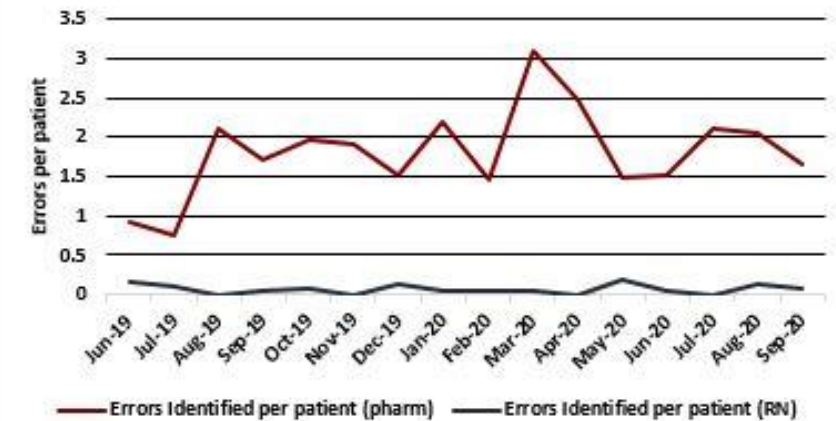
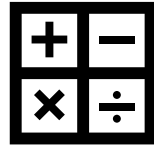


Figure 2: Errors Per Patient



Medication administration errors by nurses

Calculation errors

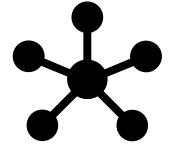


- Volumes
- Dilution, 10- or 100-fold errors
- Mixing up units
- Incorrect strength/ rate entered on infusion pumps

Wrong patient



Contributing factors



- Interruptions/distractions
- Complexity of patients' needs
- Emotional exhaustion (burnout), work stress
- Staffing inadequacy, overtime
- Poor nurse–physician relations, lack of coworker support

Common medication dispensing errors by pharmacists

Sound-alike/look-alike

Tacrolimus and tamsulosin
Prograf® and Proscar®



Selection

Formulation,
similar packaging



Interpretation and
prescription legibility



Awareness
around urgency



Expired products,
incorrect preparation



Insufficient time
for patient counselling



Workload,
lack of support staff



Patients using multiple
pharmacies

Variability in pharmacy interpretations of physician prescriptions

Methods

- Rx for 4 common meds sent to 6 different pharmacies in each of 4 US cities
 - 85 Rx for atorvastatin, alendronate, sulfamethoxazole/trimethoprim, and ibuprofen
- Sig messages gathered and compared with the written prescription

Example of physician-written prescriptions and pharmacy interpretations

Prescription Sig

Bactrim DS tabs
Take 1 tab BID
Dispense 6
Indication: UTI
No refills

Pharmacy Sig Interpretation

“Take 1 tablet by mouth twice daily for UTI.”
“Take 1 tablet by mouth twice daily for urinary tract infection.”
“Take 1 tablet by mouth 2 times a day.”
“Take 1 tablet twice daily for 3 days.”

Key omissions in dosage instructions by pharmacists

Dose frequency omitted
(e.g., “take 1 tablet for cholesterol”)

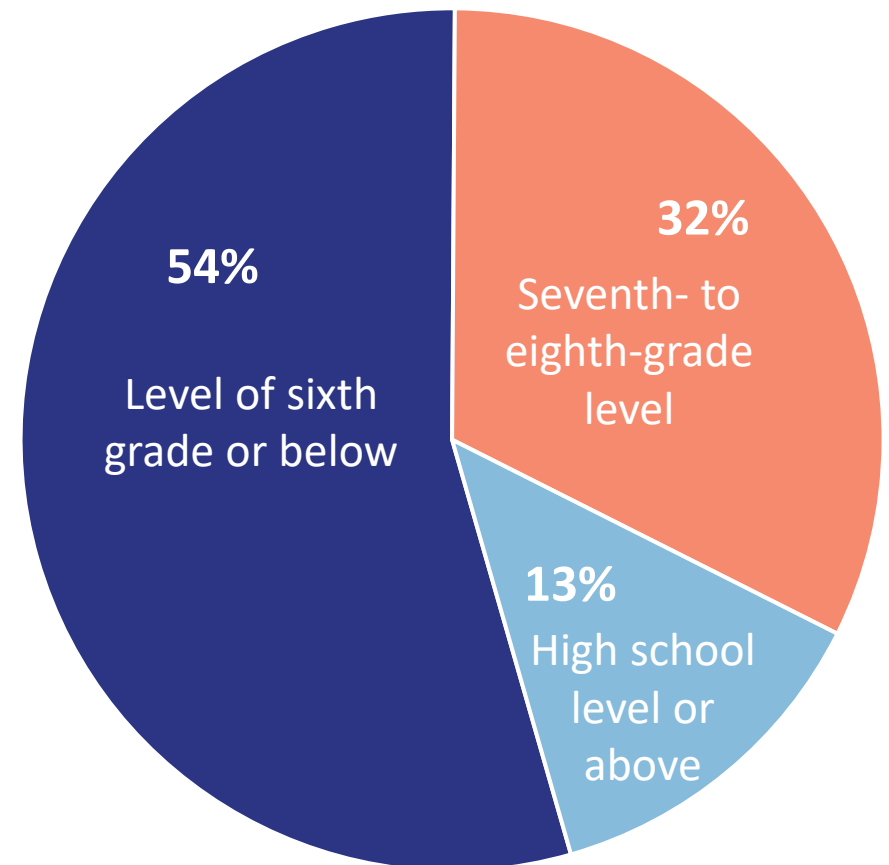
Precise timing of administration
(e.g., “in the morning”)

Transcribing indication
(e.g., high cholesterol, osteoporosis)

Spelling out acronyms
(e.g., UTI, urinary tract infection)

Instructions for use
(e.g., do not lie down for at least 20 minutes after taking)

Reading level of pharmacy instructions



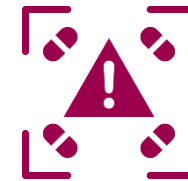
Pharmacist encounters with patients can reduce medication errors

Overview

- Prospective, blinded observational study
- Adult kidney transplant recipients ≥ 90 days post-transplant (n=237)
- Pharmacist reviewed medication history and documented medication errors discovered at the clinic visit
- Errors were categorized
- Number and type of errors were compared between patients who had a pharmacist visit vs. those who did not

Results

- **693 medication errors**



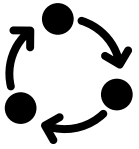
- 693 errors (3.8 errors/patient) in the group without a pharmacist encounter vs.
- 181 errors (3.1 errors/patient) in the group with a pharmacist encounter

- **Encounter group:**



- Reduction in the proportion of patients with ≥ 2 and ≥ 3 errors
- Fewer patients with errant listed medications (68% vs. 47%, $p=0.005$) and
- Few patients with lack of monitoring (39% vs. 25%, $p=0.054$)

Reducing clinician-specific medication errors (1/2)



Transitions of care

- ☐ Medication reconciliation at transitions of care
- ☐ Ideally by a pharmacist
- ☐ Clinical pharmacy services – inpatient and outpatient



Safety

- ☐ Reduced work hours
- ☐ Cultural focus on safety improvement and system error rather than individual error
- ☐ Bar coding and automation
- ☐ Automated dispensing cabinets for high-risk medications
- ☐ Infusion pumps



Multidisciplinary team

- ☐ Clinical pharmacy services (medication order review, participating in patient care rounds, and providing direct patient care and education)
- ☐ HCP working as a team and communicating effectively
- ☐ Effective prescriber to prescriber communication
- ☐ Patient counselling on dose/strength changes by multiple team members, e.g., transplant team, community pharmacist

HCP, healthcare provider.

Ciapponi A, et al. Cochrane Database of Systematic Reviews. 2021;11:1465-1858.

MacDowell P, et al. Agency for Healthcare Research and Quality 2021. <https://psnet.ahrq.gov/primer/medication-administration-errors>

Reducing clinician-specific medication errors (2/2)



Computerized prescriber order entry/clinician decision support systems

- ☐ Prioritized alerts > non-prioritized alerts



Prescription: Provide clear directions, avoid “Take as directed”

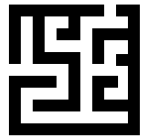
- ☐ Avoid abbreviations
- ☐ Provide indication (drugs have multiple uses, facilitates counselling)
- ☐ Provide contact information
- ☐ Encourage the use of 1 pharmacy



Feedback on prescribing errors

Summary

Medications are complicated



Transplant patients take on average 11 different medications according to a complex daily regimen



Medication errors are common and can be attributed to drug, patient, and clinician factors



Communication between team members and including the patient is critical to prevent medication errors

- Write clear prescriptions
- Ensure patient understands and is able to execute

