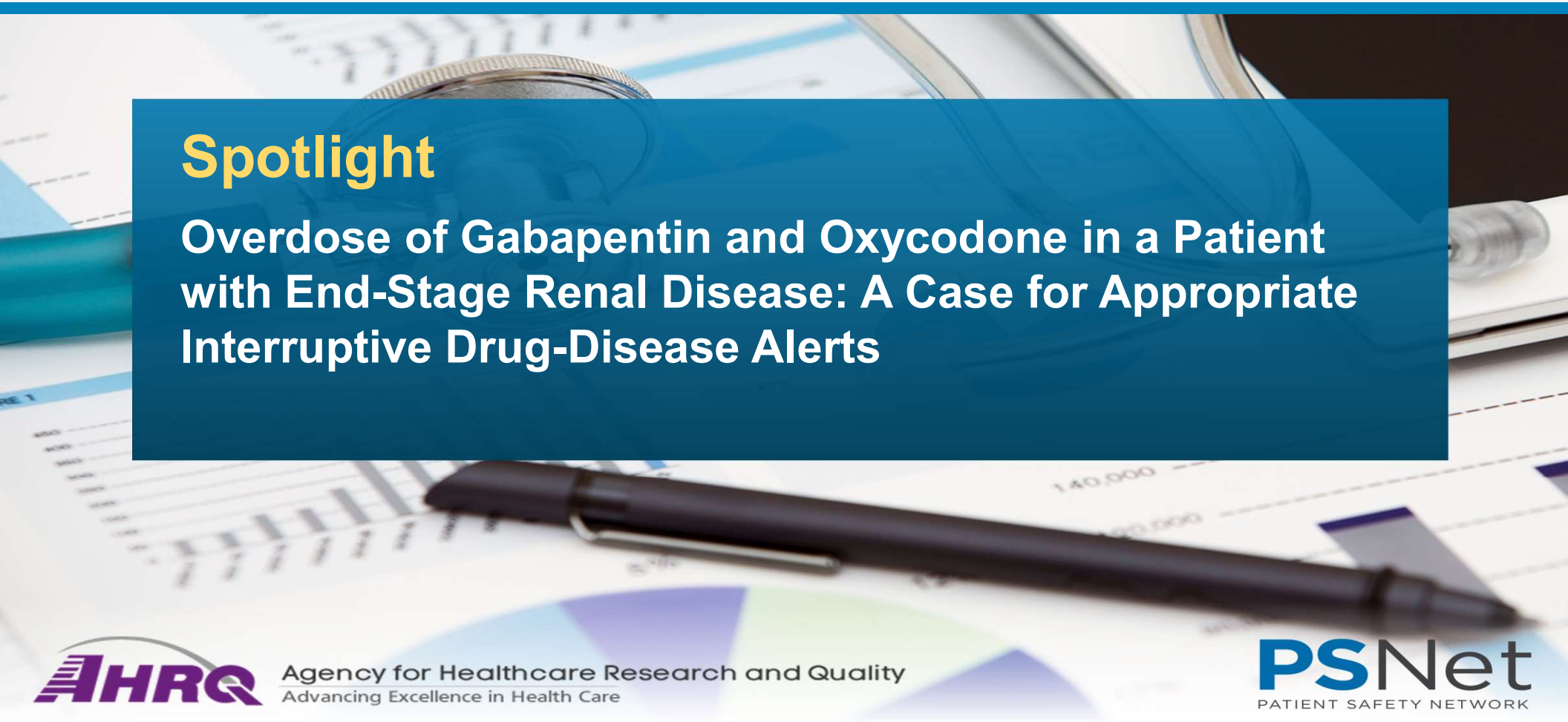
WebM&M

Morbidity and Mortality Rounds on the Web



Spotlight

Overdose of Gabapentin and Oxycodone in a Patient with End-Stage Renal Disease: A Case for Appropriate Interruptive Drug-Disease Alerts

AHRQ Agency for Healthcare Research and Quality

Advancing Excellence in Health Care

PSNet PATIENT SAFETY NETWORK

Source and Credits

- This presentation is based on the January 2023 AHRQ WebM&M Spotlight Case
  - See the full article at https://psnet.ahrq.gov/webmm
  - CME credit is available
- Commentary by: Craig Keenan, MD, Scott MacDonald, MD, Ashley Takeshita, and Dale Sapell, PharmD
- AHRQ WebM&M Editors in Chief: Patrick Romano, MD, MPH and Deb Bakerjian, PhD, APRN, RN
  - Spotlight Editors: Patrick Romano, MD, MPH and Patricia Poole, PharmD
  - Managing Editor: Meghan Weyrich, MPH

Objectives

At the conclusion of this educational activity, participants should be able to:

- Describe the signs and symptoms of gabapentin toxicity
- Recognize the need for careful dose adjustment or avoidance of commonly used medications for pain (i.e., opioids, gabapentinoids, serotonin and norepinephrine reuptake inhibitors [SNRIs], muscle relaxants, non-steroidal anti-inflammatory drugs [NSAIDs]) in patients with renal dysfunction
- Identify the opioids that are safest for use in patients with renal dysfunction
- Describe the difference between interruptive and passive alerts
- Define alert fatigue and describe its implications
- Understand the complex interaction between clinical decision-making alerts and alert fatigue
- Understand potential systems changes to reduce adverse events from drug-disease interactions

OVERDOSE OF GABAPENTIN AND OXYCODONE IN A PATIENT WITH END-STAGE RENAL DISEASE: A CASE FOR APPROPRIATE INTERRUPTIVE DRUG-DISEASE ALERTS

This case illustrates the risk of overdose of both gabapentin and opiates in the setting of end-stage renal disease

Case Details (1)

- A 38-year-old man with end-stage renal disease (ESRD) on chronic hemodialysis, type 2 diabetes, peripheral arterial disease and hypertension was admitted for nonhealing, infected lower leg wounds.
- On hospital day 2, he underwent a right below-knee amputation.
  - His postoperative course was complicated by pain at the operative stump, treated for four days with regional nerve blocks. He was also given gabapentin at 100 mg three times daily (TID), escalating to 400 mg TID by postoperative day (POD) 4.
  - Intermittent intravenous hydromorphone was also started postoperatively, which was transitioned to oral oxycodone (up to 60 mg daily) and then oral hydromorphone.
  - These dose adjustments were recommended or endorsed by a team that included surgeons, nurses, and pharmacists, and the electronic health record (EHR) did not interrupt the prescriber while entering these orders.

Case Details (2)

- On POD 7, the patient developed persistent myoclonus involving hands and arms; his gabapentin dose was decreased to 300 mg at bedtime.
- On POD 9, the patient had increasing myoclonus and severe somnolence, became arousable only with aggressive tactile stimuli, and developed hypoxia with a respiratory rate of 4 per minute. He was diagnosed with metabolic encephalopathy due to opiates and gabapentin.
  - He was treated with oxygen supplementation and intravenous naloxone with improvement in somnolence and respiratory rate (although his pain intensity also increased). He was transferred to the intensive care unit for observation and required additional naloxone due to recurrent symptoms.
- The patient's mental status returned to normal and his myoclonus resolved after dialysis and discontinuation of the gabapentin and opioids.
- However, the patient remained anxious about the possibility of recurrence of myoclonus, and rehabilitation was delayed.

OVERDOSE OF GABAPENTIN AND OXYCODONE IN A PATIENT WITH END-STAGE RENAL DISEASE: A CASE FOR APPROPRIATE INTERRUPTIVE DRUG-DISEASE ALERTS

THE COMMENTARY

By Craig Keenan, MD, Scott MacDonald, MD, Ashley Takeshita, and Dale Sapell, PharmD

WebM&M
Morbidity and Mortality Rounds on the Web

BACKGROUND

Background (1)

- Many of the most used medications to treat pain are cleared by the kidney, and thus must be carefully dosed in patients with renal dysfunction to avoid drug toxicity due to accumulation.
- This patient with ESRD developed a severe metabolic encephalopathy due to overdose of both gabapentin and opiates and failure to reduce medication doses in the setting of ESRD.
  - He received over 10 times the recommended dose of gabapentin for patients with ESRD. Similarly, oxycodone has partial renal clearance, and at least a 50-75% dose reduction is recommended for patients with advanced chronic kidney disease (CKD).
  - This error occurred despite having an experienced team caring for the patient daily who did not notice the potential danger from escalating doses of these medications over several days, until the patient developed severe myoclonus and oversedation.

Background (2)

- Most American hospitals now have a robust EHR with drug-disease interaction checking software that should prompt the prescriber to consider dose adjustment in patients with CKD.
- However, drug-disease alerts are often passive (meaning the clinician must decide to go to the drug interactions section to see alerts “on demand”) versus interruptive (where the alert appears on the screen and the clinician must act on the alert to complete the workflow).
- In many EHRs, such alerts are turned off or made passive to avoid "alert fatigue," which is a cognitive state that occurs when clinicians have experienced high volumes of alerts and stop paying attention to subsequent alerts.
- This has a greater chance of occurring if a large proportion of alerts are not relevant or clinically important. However, even appropriate interruptions require mental effort for evaluation, and can cause fatigue and an increase in overriding the recommendations.

REVIEW OF ANALGESICS IN RENAL DYSFUNCTION

Review of Analgesics in Renal Dysfunction (1)

- Chronic pain has an estimated prevalence of 50-80% among adults with CKD on hemodialysis (HD).[1] This patient also had acute, persistent postoperative pain after a below-knee amputation.
- However, pharmacological pain management options are limited due to altered pharmacokinetics in patients with CKD, as seen in this case.
- Therefore, the use and safety of commonly prescribed analgesic agents in the setting of renal dysfunction are reviewed below.

Review of Analgesics in Renal Dysfunction (Gabapentinoids) (1)

- **Gabapentin** and **pregabalin** are frequently used agents for neuropathic pain.
- Unique to the CKD patient population, gabapentin is also used off-label for uremic pruritis.[2] A 2016 study reported that 6-9% of patients with CKD received a prescription for gabapentinoids.[3]
- Both gabapentin and pregabalin are predominantly excreted by the kidneys. Renal impairment can lead to accumulation of both medications, which can lead to serious toxicities.
  - Therefore, it is critical to monitor renal function and possible side effects in patients with CKD receiving gabapentinoids.
  - Prompt dose adjustments should be made based on renal function
- Patients with ESRD on hemodialysis should receive gabapentin after dialysis due to removal of gabapentin through dialysate.

Review of Analgesics in Renal Dysfunction (Gabapentinoids) (2)

Table 1. Oral Gabapentinoid Dose Adjustments in Renal Dysfunction

	Maximum Daily Dose (based on manufacturer's labeling)	
CrCl (mL/minute)	**Gabapentin[9]**	**Pregabalin[10]**
> 79	3,600 mg/day in 3 divided doses	600 mg/day in 2 to 3 divided doses
60 to 79	1,800 mg/day in 3 divided doses	
50 to 59		300 mg/day in 2 to 3 divided doses
30 to 49	900 mg/day in 2 to 3 divided doses	
15 to 29	600 mg/day in 1 to 2 divided doses	150 mg/day in 1 to 2 divided doses
< 15	300 mg/day in 1 dose (3 times weekly after hemodialysis)	75 mg/day in 1 dose (3 times weekly after hemodialysis)

CrCl=creatinine clearance

There is no universally accepted dosing regimen for patients on hemodialysis, but a conservative approach of 100 mg by mouth three times weekly after hemodialysis, up to 300 mg three times weekly after hemodialysis, is appropriate.[4,5]

Review of Analgesics in Renal Dysfunction (Gabapentinoids) (3)

- Gabapentin toxicity can present as changes in mental status, drowsiness, and myoclonus. [6,7]
- These neurological toxicities are usually reversible with dialysis or renal replacement therapy.[8]
- In this case involving lower doses of gabapentin, prompt discontinuation of the medication accompanied by dialysis led to reversal of the toxicity.

Review of Analgesics in Renal Dysfunction (Opioids) (1)

Recommendations for opioid dosing in renal insufficiency vary across products

Table 2. Opioids in Renal Dysfunction[13]

Safety in Renal Dysfunction	Opioid	Starting Dose (opioid naïve patients)	Dialyzable
Recommended	Hydromorphone	1-2 mg oral every 4 h as needed	Yes
	Buprenorphine	5 mcg/h transdermal patch every 7 d	No
	Methadone	Consult pain specialist	No
	Fentanyl	Consult pain specialist	No
Use with Caution	Oxycodone	2.5 mg oral every 4 h as needed	No data
Avoid	Morphine	5-10 mg every 4 h as needed	Yes
	Hydrocodone	10 mg every 4 h as needed	No data

d=days; h=hours

Review of Analgesics in Renal Dysfunction (Opioids) (2)

- Although **morphine** is one of the most extensively used opioids, it has an active metabolite (morphine-6-glucuronide (M6G)) that is excreted through renal elimination.
- The accumulation of M6G in patients with renal dysfunction increases the risk of toxicity, manifesting as confusion, sedation, myoclonus, and respiratory depression.[11]
- Due to these increased risks, morphine is not recommended in patients with moderate to severe renal impairment or those on hemodialysis.[12]

Review of Analgesics in Renal Dysfunction (Opioids) (3)

- **Oxycodone** is another opioid commonly prescribed for the management of pain.
- Less than 10% of the parent compound is excreted unchanged in the urine, and toxicity can occur due to accumulation of the parent drug and its metabolites in the setting of renal dysfunction, as was seen with this case.
- Oxycodone is considered a second-line therapy compared with other opioids and may be used with caution and close monitoring in patients with CKD. [12]

Review of Analgesics in Renal Dysfunction (Opioids) (4)

- **Buprenorphine**, **fentanyl**, **methadone**, and **hydromorphone** are considered the safest opioids in patients with renal impairment due to minimal risk of accumulation.[12,13]
  - However, methadone should be used cautiously in opioid naïve patients due to its high potency, interpatient pharmacokinetic variability, and long-half life.
  - Transdermal fentanyl does not have active metabolites and is considered safe in renal dysfunction; however, use is limited to opioid tolerant patients.
- Therefore, buprenorphine and hydromorphone are considered first-line in the management of pain in patients with renal insufficiency.[13]
  - To reduce the risk of opioid-related adverse effects among these patients, prescribers should initiate low doses and titrate slowly, extend the dosing interval, avoid long-acting formulations, and monitor patients closely for side effects.

Review of Analgesics in Renal Dysfunction (SNRIs) (1)

- Serotonin and norepinephrine reuptake inhibitors (SNRIs) – **duloxetine** and **venlafaxine** – are often used to treat neuropathic pain.
- Duloxetine should be avoided in patients with ESRD or severe renal impairment (creatine clearance or CrCl < 30mL/min) due to increased concentrations of inactive metabolites.[14]
  - Duloxetine should also be avoided in patients with hepatic insufficiency due to decreased metabolism and elimination, which may result in drug accumulation.

Review of Analgesics in Renal Dysfunction (SNRIs) (2)

- **Venlafaxine** is hepatically metabolized via CYP2D6 and is primarily excreted renally.
- Dosing should be adjusted with renal impairment due to the potential for prolonged half-life of both the parent drug and active metabolites.[15]
  - In mild and moderate (CrCl = 30-89 mL/min) renal impairment, the total daily dose should be reduced by 25-50%.
  - The total daily dose should be reduced by 50% or more in patients with severe (CrCl < 30 mL/min) renal impairment.[16]
  - Dose adjustments are also required in the setting of hepatic impairment.
  - Without appropriate renal dose adjustments, both duloxetine and venlafaxine can accumulate and exacerbate adverse events including hypertension, nausea, insomnia, dizziness, and serotonin syndrome. Venlafaxine is preferred over duloxetine in patients with CKD due to its reduced risk of drug accumulation.

Review of Analgesics in Renal Dysfunction (Muscle Relaxants) (1)

- Muscle relaxants, including **baclofen**, **tizanidine**, **cyclobenzaprine**, and **methocarbamol**, are commonly used as adjunctive treatments for pain.
- Most are not indicated for long-term use due to a paucity of data supporting prolonged use and the risk of serious adverse effects including dizziness, drowsiness, sedation, and confusion.[17]

Review of Analgesics in Renal Dysfunction (Muscle Relaxants) (2)

- Baclofen is often prescribed for spasticity and musculoskeletal pain,[18] but more than 70% is excreted as unchanged drug in the urine.
- Dose adjustments should be made for patients with CrCl < 80 mL/min.

Table 3. Oral Baclofen Dose Adjustments in Renal Dysfunction[20]

CrCL (mL/min)	Dose
> 80	5 mg every 8 hours
50-80	5 mg every 12 hours
30-50	2.5 mg every 8 hours
< 30	Avoid use

CrCl=creatinine clearance

Review of Analgesics in Renal Dysfunction (Muscle Relaxants) (3)

- Failure to adjust the baclofen dose in the setting of renal insufficiency may increase the risk of encephalopathy, delirium, and hospitalization.[18]
- Additionally, baclofen use in patients on dialysis has been shown to increase the risk of hospitalization, mortality, and CNS adverse effects such as encephalopathy and delirium.[19]
- Therefore, use in patients on hemodialysis should be avoided.

Review of Analgesics in Renal Dysfunction (NSAIDs) (1)

- Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used as pain relievers or anti-inflammatory agents.
- Their use in renal dysfunction, however, is limited due to the risk of NSAID-related kidney injury.
  - NSAIDs block the production of prostaglandins, which are important for vasodilation of the afferent arteriole in the kidney to preserve renal blood flow. The inhibition of prostaglandins constricts the afferent arteriole, which can lead to hypertension, hyperkalemia, hypervolemia, acute kidney injury, and worsening of renal function.[21]
- Use of NSAIDs in renal impairment is dependent on multiple factors including, but not limited to, type of pain, dose and duration of therapy, and individual risk-benefit analysis.

Review of Analgesics in Renal Dysfunction (NSAIDs) (2)

- In patients with CKD, the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines do not recommend prolonged therapy with NSAIDs in patients with CrCl < 60 mL/min and suggest avoiding NSAIDs in patients with CrCl < 30 mL/min.[22]
- The lowest effective dose, shortest duration possible, and shorter-acting agents are preferred if systemic NSAID use is deemed necessary.
- Topical NSAIDs such as diclofenac gel have reduced systemic absorption compared to their oral counterparts, and thus have significantly lower renal adverse effects.
- As such, topical agents should be considered in patients with CKD who have musculoskeletal and arthritic pain, with monitoring of renal function.[23]

APPROACH TO IMPROVING PATIENT SAFETY

Approach to Improving Patient Safety (1)

- Computerized clinical decision support (CDS) provides timely patient-specific information, usually at the point of care, to help inform decisions about a patient's treatment.
- Medication-related CDS in electronic health records (EHRs) is specifically intended to reduce prescribing errors and adverse drug events by guiding prescribers during computerized order entry.
- Medication-related CDS includes alerts that advise prescribers on dosing, allergies, drug interactions, diseases, pregnancy, lactation, and age.
- However, too many alerts may lead to alert fatigue, with EHR users habitually overriding alerts without reviewing them, simply to get through their work, regardless of clinical importance.

Approach to Improving Patient Safety (2)

- As EHRs began to be more universally accepted in the early 2000s, there were high hopes for CDS to significantly reduce prescribing errors.
- Early studies of home-grown EHR systems with highly customized CDS alerts did prove somewhat effective. But now most EHRs are from commercial vendors and rely on medication and alert databases from separate vendors.
  - This complexity makes CDS more difficult to customize.
  - A recent study of one of these commercial EHRs at Brigham and Women's Hospital evaluated the vendor-provided renal medication-related CDS alerts. Nearly 90% of the alerts indicating that "specific dosing guidelines are not available for this patient's level of renal impairment" were classified as inappropriate, and 100% of these alerts were overridden by the prescribers, illustrating a failure of trust in the system.

Approach to Improving Patient Safety (3)

- Drug-disease alerts, unlike drug-drug interaction alerts, pose unique difficulties for implementation.
- They rely on an accurate problem list to identify the disease(s) of interest.
  - Problem lists may not be complete, so appropriate alerts may not be activated.
  - Problem list entries may be out of date and the disease may have resolved or progressed, which may increase or decrease the appropriateness of an alert.
  - Entries may not contain information on disease severity (such as GFR level) necessary to focus alerts on those scenarios most likely to cause risk.
- In the case of alerts for CKD, the EHR could instead use the most recent creatinine via a separate, custom CDS mechanism.
- However, these data may not exist, may be out of date, may identify acute kidney disease rather than chronic disease, and may not identify all dialysis patients—potentially leading to inappropriate alerts or failure to alert.

Approach to Improving Patient Safety (4)

- If the CDS uses more inclusive yet less specific criteria, more drug-disease alerts would ensue, leading to high volumes of less specific, inappropriate alerts.
- For example, drug dosing alerts (for any mention of CKD) may fire for patients with CKD Stage 1, where dose adjustment is not necessary, thus contributing to alert fatigue, and overrides of future alerts.
- Custom renal dose warnings can be labor-intensive to build and maintain in an EHR system. In many systems, customizations are overwritten during database updates, and would need to be reconfigured on a regular basis.

Approach to Improving Patient Safety (5)

- To reduce alert fatigue and provider dissatisfaction with the EHR, many institutions have set their systems to deactivate many of the available alerts, make the alerts less interruptive (e.g., passively providing advice without need for acknowledgment), or provide alerts only “On Demand”, whereby the clinician can look at the decision support recommendations if they choose to do so.
- These settings are typically chosen to reduce the large number of alerts that would fire if the EHR provided alerts for every drug-disease interaction, to avoid alert fatigue, and to improve the efficiency of clinicians’ work.

Approach to Improving Patient Safety (6)

- Health systems can license additional software that enables more customization, but at additional cost.
- For example, Kaiser Permanente in California worked with their drug-disease knowledge software vendor, physicians and pharmacists to iteratively decide which drug-disease alerts to enable. Implementation led to a dramatic reduction in drug-disease alerts, and the chosen alerts were well received by the prescribers, but significant time and effort were required for development and maintenance.[24]

Approach to Improving Patient Safety (7)

- Other potential methods to reduce dosing errors in renal disease are to include the estimated GFR on the order screen, to create a suite of medication-specific dosing alerts, or to create specific pain medication order sets to guide clinicians through appropriate medications and doses.
- These methods, however, rely the clinician to actively do something on their own without any behavioral nudge to do so (e.g., acknowledge the elevated creatinine and react, or choose to open the order set), which will perpetuate wide variability in clinical practice.

Approach to Improving Patient Safety (8)

- Beyond medication alerts, in the EHR "ecosystem," there are frequently many additional types of alerts, such as sepsis alerts and cancer screening or immunization reminders, which can contribute to alert fatigue.
- Much research is ongoing to learn how to optimize alerts to reduce fatigue.
- Health systems can also work to optimize their alerts, through a process described as "Alert Stewardship".
  - This approach entails having governance for initiation of new alerts and monitoring the impact of alerts on clinical processes and outcomes.
  - With such stewardship, ineffective CDS should be rebuilt or discontinued to protect the effectiveness of the remaining alerts.
  - In the coming years, vendors should provide tools, and healthcare organizations should use them, to thoughtfully enable drug-disease alerts so clinicians can optimize each patient's prescribed medications while guarding against alert fatigue.

TAKE HOME POINTS

Take-Home Points

- In patients with renal dysfunction, careful selection and dose adjustment of medications must be undertaken for many medications, including medications to treat pain.
- Configuring drug-disease alerts in EHRs is complex, as available software often leads to excessive unimportant alerts and contributes to alert fatigue.
- Customization of alerts is not readily available in many EHR systems without significant human and/or monetary resources.
- Devoting human resources to monitoring the performance and override rates of alerts in CDS (i.e., alert stewardship) is important to optimize CDS effectiveness.

REFERENCES

References

1. Tobin DG, Lockwood MB, Kimmel PL, et al. Opioids for chronic pain management in patients with dialysis-dependent kidney failure. *Nat Rev Nephrol*. 2022;18(2):113-128. [Free full text]
2. Nofal E, Farag F, Nofal A, et al. Gabapentin: A promising therapy for uremic pruritus in hemodialysis patients: A randomized-controlled trial and review of literature. *J Dermatolog Treat*. 2016;27(6):515-519. [Available at]
3. Novick TK, Surapaneni A, Shin JI, et al. Prevalence of opioid, gabapentinoid, and NSAID use in patients with CKD. *Clin J Am Soc Nephrol*. 2018;13(12):1886-1888. [Free full text]
4. Gunal AI, Ozalp G, Yoldas TK, et al. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. *Nephrol Dial Transplant*. 2004;19(12):3137-3139. [Free full text]
5. Atalay H, Solak Y, Biyik Z, et al. Cross-over, open-label trial of the effects of gabapentin versus pregabalin on painful peripheral neuropathy and health-related quality of life in haemodialysis patients. *Clin Drug Investig*. 2013;33(6):401-408. [Free full text]
6. Bookwalter T, Gitlin M. Gabapentin-induced neurologic toxicities. *Pharmacotherapy*. 2005;25(12):1817-1819. [Available at]
7. Jones H, Aguila E, Farber HW. Gabapentin toxicity requiring intubation in a patient receiving long-term hemodialysis. *Ann Intern Med*. 2002;137(1):74. [Free full text]
8. Miller A, Price G. Gabapentin toxicity in renal failure: the importance of dose adjustment. *Pain Med*. 2009;10(1):190-192. [Free full text]
9. Neurontin [full prescribing information]. New York, NY: Pfizer, 2017. Accessed December 2022. [Free full text]
10. Lyrica [full prescribing information]. New York, NY: Pfizer, 2020. Accessed December 15, 2022 [Free full text]
11. Klimas R, Mikus G. Morphine-6-glucuronide is responsible for the analgesic effect after morphine administration: a quantitative review of morphine, morphine-6-glucuronide, and morphine-3-glucuronide. *Br J Anaesth*. 2014;113(6):935-944. [Free full text]
12. Owsiany MT, Hawley CE, Triantafylidis LK, et al. Opioid management in older adults with chronic kidney disease: a review. *Am J Med*. 2019;132(12):1386-1393. [Free full text]
13. Corona AG, Garcia P, Gelfand SL. Palliative care for patients with cancer and kidney disease. *Adv Chronic Kidney Dis*. 2022;29(2):201-207.e1. [Available at]
14. Cymbalta [full prescribing information]. Indianapolis, IN: Lilly USA, LLC, 2021. Accessed December 15, 2022. [Free full text]
15. Mathew RO, Bettinger JJ, Wegrzyn EL, et al. Pharmacotherapeutic considerations for chronic pain in chronic kidney and end-stage renal disease. *J Pain Res*. 2016;9:1191-1195. [Free full text]

References

16. Effexor [full prescribing information]. Philadelphia, PA: Pfizer, 2022. Accessed December 15, 2022. [Free full text]
17. Soprano SE, Hennessy S, Bilker WB, et al. Assessment of physician prescribing of muscle relaxants in the United States, 2005-2016. *JAMA Netw Open*. 2020;3(6):e207664. [Free full text]
18. Muanda FT, Weir MA, Bathini L, et al. Association of baclofen with encephalopathy in patients with chronic kidney disease. *JAMA*. 2019;322(20):1987-1995. [Free full text]
19. Chauvin KJ, Blake PG, Garg AX, et al. Baclofen has a risk of encephalopathy in older adults receiving dialysis. *Kidney Int*. 2020;98(4):979-988. [Available at]
20. El-Husseini A, Sabucedo A, Lamarche J, et al. Baclofen toxicity in patients with advanced nephropathy: proposal for new labeling. *Am J Nephrol*. 2011;34(6):491-495. [Free full text]
21. Lucas GNC, Leitão ACC, Alencar RL, et al. Pathophysiological aspects of nephropathy caused by non-steroidal anti-inflammatory drugs. *J Bras Nefrol*. 2019;41(1):124-130. [Free full text]
22. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Updated January 2013. Accessed May 17, 2021. [Free full text [PDF)]
23. Baker M, Perazella MA. NSAIDs in CKD: Are they safe? *Am J Kidney D*. 2020:76(4)546-557. [Free full text]
24. Bubp JL, Park MA, Kapusknik-Uner J, et al. Successful deployment of drug-disease interaction clinical decision support across multiple Kaiser Permanente regions. *J Am Med Inform Assoc*. 2019; 26(10):905-910. [Free full text]