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Pharmacist's Comprehensive Medication Review in Deprescribing Chronic Medications at the End of Life

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Abstract

Appropriate medication management is essential to improve quality of life for patients with terminal illness. Individuals under hospice care are vulnerable to adverse drug events due to their terminal disease, multi-organ failure, and polypharmacy. Pharmacists are essential partners when it comes to participating in the care of hospice patients with complex medication regimens and to identifying treatments tailored to each patient. The purpose of this case report is to demonstrate the value of a pharmacist's comprehensive medication review, assisted by a clinical decision support system, in deprescribing certain chronic medications for a patient in hospice care who had been chronically experiencing alternating episodes of constipation and diarrhea. This case describes a 64-year-old male with stage IV metastatic lung cancer who was presented to a pharmacist to complete a comprehensive medication review. Upon reviewing the patient's medical history, goals of care, and medications, the pharmacist recommended to discontinue 1) aspirin to mitigate risk of gastrointestinal bleed; 2) simvastatin to improve quality of life and mitigate a Cytochrome P450 (CYP) 3A4 drug-drug interaction (DDI); 3) lactulose to mitigate risk of gastrointestinal side effects; 4) duloxetine to mitigate a CYP2D6 DDI; and 5) furosemide due to ineffective dose. The provider and the patient agreed to discontinue aspirin, simvastatin, and lactulose. The provider also deprescribed duloxetine and furosemide based on the pharmacist's previous recommendations, and all discontinued medications were not restarted. Five months later, the patient reported to be doing well and continuing his weekly physical therapy sessions for gait and mobility.

Keywords: Cancer; Clinical Decision Support System; Deprescribing; Drug–Drug Interaction; Pharmacist; Hospice

Introduction

Pharmacist involvement in hospice care has been expanding significantly due, in part, to increasing specialized training programs and board certification opportunities [1]. Hospice care focuses on the quality of life, comfort, and care for individuals with terminal illness and those approaching the end of life [2]. Hospice care is tailored to the patient's terminal illness, symptomatic relief, and medication regimen [2]. Pharmacists bring value by performing comprehensive medication reviews and recommending adjustments to the medication regimen by honing in on curative and/or chronic medications and deprescribing unnecessary medications [2]. Studies have indicated that discontinuing chronic medications (*e.g.,* antihypertensive, statin, bisphosphonates) at the end of life decreases the risk of ADEs and reduces costs without worsening clinical outcomes [3-6]. ADEs negatively impact

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the quality of life for hospice patients, and DDIs can further increase the risk of ADEs [7]. Pharmacist-led comprehensive medication reviews that consider pharmacokinetic and pharmacodynamic concepts, with the help from a CDSS [8], can reduce the risk of ADEs [8-10]. The objective of this case report is to demonstrate that a pharmacist-led comprehensive medication review can lead to the mitigation of DDIs, reduce ADE risk, and result in the deprescribing of chronic medications that will not provide benefit within the predicted life expectancy.

Case Presentation

A 64-year-old male hospice patient presented to his healthcare provider with a medication risk score (MRS) classified as "high" and a medical history that included stage IV metastatic lung cancer, cardiomyopathy, spinal stenosis, and gastrointestinal bleed. The pharmacist reviewed the patient's medical history and evaluated the appropriateness of his current medication regimen (Table 1) while considering the patient's goals of care. The pharmacist's recommendations can be found in Table 2; however, only recommendations that targeted deprescribing of chronic medications will be discussed in detail within this case report.

With assistance from the CDSS, the pharmacist identified a DDI affecting metoprolol and oxycodone perpetrated by duloxetine at CYP2D6. The plasma concentration of metoprolol was likely to be higher than predicted, increasing the risk of ADEs (*e.g.,* hypotension, bradycardia). Of note, the patient's heart rate and blood pressure were stable at the time of review. In addition to metoprolol, plasma concentrations of oxycodone were likely to be higher than expected, increasing the risk of ADEs. The plasma concentrations of oxycodone's active metabolite, oxymorphone, was likely to be lower, thereby increasing the likelihood for pharmacotherapy failure (*e.g.*, ineffective pain control). The patient had been scoring an average pain score of 8 based on the numeric rating scale (NRS), mainly attributing to his terminal illness, which was perceived by the patient to be relatively controlled. The pharmacist also identified a DDI at CYP3A4 affecting oxycodone perpetrated by simvastatin. The plasma concentration of oxycodone was likely to be higher than expected due to the DDI, thereby increasing the likelihood of side effects (*e.g.,* sedation, constipation) and ADEs (*e.g.,* respiratory depression) for oxycodone, which may explain, in part, the patient's chronic constipation [11,12]. Based on these findings alone, continued use of simvastatin and duloxetine was not beneficial for the patient's quality of life, and the pharmacist recommended to discontinue these medications. With the deprescribing of simvastatin and duloxetine, the patient was further monitored for subsequent changes in pain control and side effects.

Moreover, the pharmacist addressed the appropriateness of other medications (*i.e.,* aspirin, lactulose, furosemide). During a telephonic consultation, in addition to deprescribing simvastatin, the provider agreed to deprescribe aspirin due to lack of long-term clinical benefit and the increased risk of bleeding in older adults for primary prevention of cardiovascular disease (CVD). Lactulose was also

Table 1: Patient's medication list at the time of pharmacist's medication review.

Condition	Medication	Dose	Directions
Benign prostatic hyperplasia	Tamsulosin	0.4 mg	1 capsule in the morning
Cardiomyopathy	Furosemide	20 mg	1/2 tablet in the morning
Constipation	Lactulose	10 g/15 mL	2 teaspoons as needed
	Sennosides/docusate	8.6 mg – 50 mg	2 tablets daily at bedtime
COPD	Umeclidinium bromide	62.5 mcg	1 puff in the morning
GERD	Pantoprazole	40 mg	1 tablet in the morning
Hyperlipidemia	Simvastatin	20 mg	1 tablet at bedtime
Hypertension	Metoprolol succinate	50 mg	1 tablet in the morning
Hypokalemia	Potassium chloride	8 mEq	1 tablet in the morning
Nausea	Ondansetron	4 mg	1 tablet as needed
Nutrient deficiency	Multivitamin	N/A	1 tablet in the morning
Pain	Oxycodone	10 mg	1 tablet in the morning, noon, evening, and bedtime
Primary prevention of ASCVD	Aspirin	81 mg	1 tablet in the morning
Seizure	Levetiracetam	500 mg	1 tablet in the morning and evening
Spinal stenosis	Acetaminophen	325 mg	1 tablet in the morning, noon, evening, and bedtime
	Duloxetine	20 mg	1 capsule in the morning
	Pregabalin	150 mg	1 capsule in the morning, evening, and bedtime

Abbreviations: ASCVD- Atherosclerotic Cardiovascular Disease; COPD- Chronic Obstructive Pulmonary Disease; GERD- Gastroesophageal Reflux Disease.

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Table 2: Pharmacist's recommendations and implementations during medication review.

Medication	Pharmacist's Recommendation	Implementation
Aspirin 81 mg	Discontinue aspirin to mitigate gastrointestinal bleed risk	Aspirin discontinued
Duloxetine 20 mg	Discontinue to mitigate competitive inhibition at CYP2D6	Duloxetine discontinued
Furosemide 20 mg	Discontinue due to ineffective dose	Furosemide discontinued
Lactulose 10 g / 15 mL	Discontinue lactulose to minimize risk of gastrointestinal distress	Lactulose discontinued
Pregabalin 150 mg	Monitor renal clearance and adjust dose if necessary	Renal function was normal
Sennosides-docusate 8.6 mg /50 mg	Switch to a first-line medication for constipation (*e.g.,* PEG)	Patient declined
Simvastatin 20 mg	Discontinue to mitigate competitive inhibition at CYP3A4 and due to lack of evidence for statin use at the end of life	Simvastatin discontinued

discontinued due to its unfavorable gastrointestinal side effect profile, given the patient's decreased appetite and emaciated state due to cancer. The provider and patient decided to continue sennosides/docusate, which was sufficiently managing the patient's constipation. Although the provider was not opposed to discontinuing duloxetine and furosemide, the patient did not accept these specific recommendations initially. Five months later, the provider deprescribed duloxetine, due to lack of clinical efficacy for spinal stenosis. Additionally, the provider deprescribed furosemide due to ineffective dose and absence of clinical indication (*i.e.,* edema). At this time, the patient's MRS decreased from "high" to "moderate," which was attributed to mitigated DDIs, as well as the discontinuation of duloxetine, a medication with a sedative burden. Overall, the patient reported to be doing well with the medication regimen adjustments without pain. The patient's vitals and lab values (*i.e.,* blood pressure, cholesterol) were within normal limits at follow-up as well.

Discussion

In the last year of life, the number of medications prescribed increases by 50%, which may increase the burden on patients and decrease their quality of life [13]. Since it may be challenging to discern certain chronic medications that can be safely deprescribed in a hospice patient, the involvement of a pharmacist can be valuable in the effort to reduce pill burden and ADEs, while simultaneously preserving quality of life [13]. For decades, low-dose aspirin (75 – 100 mg) has been widely prescribed for primary and secondary CVD prevention [14]. In April 2022, the U.S. Preventive Services Task Force (USPSTF) released new recommendations on aspirin therapy for the primary prevention of CVD in adults. In the latest guidance, USPSTF concluded initiating aspirin for primary prevention in ages 60 years or older may have no net benefit [14]. In addition, emerging evidence indicates that the discontinuation of aspirin does not result in increased ischemic risk [15]. Compared to some of the first trials in the 1980s that demonstrated aspirin efficacy, participants in modern aspirin trials generally have higher statin and antihypertensive use [15]. Additionally, recent data indicates that the efficacy of aspirin may only be evident earlier on, within the first month after a cardiovascular index event [15]. Thus, patients today might not obtain similar cardiovascular protection from aspirin compared to assumptions based on earlier evidence [15]. Lastly, the absolute risk of bleeding increases with age; therefore, older adults and individuals with higher risk for bleeding (e.g., concomitant anticoagulants, history of bleeding) may be ideal candidates for discontinuation of aspirin [14]. After aspirin is initiated, the net benefit becomes progressively smaller with advancing age due to an increased risk of bleeding [14]. Given the patient's history of gastrointestinal bleed and limited duration of efficacy, aspirin for chronic primary prevention was not appropriate for continuation in the setting of hospice care, and the provider accepted the pharmacist's recommendation to deprescribe.

Like aspirin, statins are also commonly prescribed for primary or secondary prevention of CVD [16]. Despite questionable clinical benefit in patients with limited life expectancy, many patients take statins in the last year of life [17]. When statins are used to reduce the risk of CVD for primary or secondary prevention, it takes approximately over two years for clinical benefits to accrue [18]. Therefore, statin therapy is often considered for discontinuation in the setting of advanced life-limiting disease [17]. In this case, the patient was taking simvastatin, which undergoes metabolism by the CYP3A4 isoenzyme [19]. The CDSS identified simvastatin as a medication with stronger affinity for the CYP3A4 enzyme than oxycodone (Table 3). This DDI causes the plasma concentration of oxycodone to be higher than expected [20]. As a result, the patient is more likely to experience side effects from oxycodone, which may explain, in part, why he had been taking daily stool softener and laxative for constipation. Given the lack of benefit of a statin at the end of life and presence of the DDI at CYP3A4, simvastatin was deprescribed as the risks outweighed the benefits.

While constipation may have been a side effect from oxycodone, it is also a highly prevalent and distressing symptom in patients with terminal illness, and pharmacists can play an important role in preventing and managing debilitating symptoms of constipation [21]. Although nonpharmacologic measures (*e.g.,* adequate fluid and fiber intake) may provide benefit, concomitant pharmacological treatment is often

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Table 3: Summary of affinity and CYP450 metabolic pathway.

Substance	CYP1A2	CYP2C19	CYP2D6	CYP3A4
Acetaminophen				
Duloxetine				
Metoprolol				
Ondansetron				
Oxycodone			*	
Pantoprazole				
Simvastatin				
Tamsulosin				
Affinity Strengths	Weak Substrate		Medium Substrate	

Abbreviations: Only CYP-metabolized oral medications are displayed; CYP- Cytochrome P450; *- Prodrug.

necessary to alleviate constipation in patients with advanced illness [21]. The treatment of constipation in hospice care is uncertain, and available studies have mainly focused on patients with chronic constipation, rather than those with terminal illness [21]. According to the American College of Gastroenterologists, osmotic laxatives (*e.g.,* polyethylene glycol [PEG], lactulose) have the strongest evidence for improving stool frequency and consistency in patients with chronic constipation [21]. Although lactulose has proven to be more effective than placebo in clinical trials, it is not considered a first-line option for constipation due to its unfavorable side effect profile (*e.g.*, flatulence, bloating, nausea, and diarrhea) [22,23]. On the other hand, PEG has consistently proven to be effective in the treatment of constipation with fewer ADEs [24]. According to a meta-analysis of studies that compared PEG and lactulose for the treatment of chronic constipation in adults up to 75 years of age, PEG was more efficacious (*e.g.,* stool frequency, abdominal pain) [24]. In addition to the lactulose, the patient was prescribed sennosides/docusate daily for chronic constipation. Randomized controlled trials have shown benefit of stool softeners, such as docusate, over placebo in adults with constipation [25]. However, recent evidence has indicated that there is no significant benefit of docusate with sennosides compared with placebo in hospice patients with constipation [26]. Although the pharmacist recommended to use PEG as first-line therapy, the provider and patient decided to continue sennosides/docusate, which was sufficiently managing the patient's constipation. As the pharmacist recommended, lactulose was discontinued due to its gastrointestinal side effect profile, which was unfavorable for the patient who presented with decreased appetite and weight loss due to his cancer and chemotherapy.

Debilitating pain is also commonly experienced by hospice patients, and effective pain management is important in improving quality of life [27]. The World Health Organization pain ladder offers a stepwise guideline for pain management, which begins with non-opioid medications (e.g., non-steroidal anti-inflammatory drugs) then progresses to opioids for refractory pain [28]. For patients with terminal illness, opioid therapies often provide the greatest analgesic relief [27]. However, the use of opioids requires careful dosing and monitoring due to potential ADEs (e.g., respiratory depression) [29]. Adjuvant therapies such as anticonvulsants, tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) are used to specifically manage neuropathic pain [28]. The patient in this case was taking duloxetine and oxycodone for chronic pain that was associated with spinal stenosis and cancer. While duloxetine, a SNRI, has demonstrated clinical efficacy for pain subtypes such as diabetic peripheral neuropathic pain and fibromyalgia, there is currently a lack of evidence for its efficacy in spinal stenosis [30]. Analgesic medications are often combined with physical therapy to manage spinal stenosis, however, there is limited evidence to guide medication treatment with certainty [31]. Gabapentinoids (*e.g.,* gabapentin, pregabalin) have been shown to improve pain scores and increase walking distances in patients with spinal stenosis [31]. Given the lack of clinical evidence or presence of a comorbid mood disorder, the pharmacist recommended to discontinue duloxetine and to continue use of pregabalin with ongoing physical therapy to manage spinal stenosis. Although the provider accepted this recommendation, duloxetine was not immediately deprescribed because the patient's pain was under control, and he wished to remain on the medication. Upon follow-up, the provider and patient agreed to discontinue duloxetine, based on the pharmacist's previous rationale.

In addition to the lack of benefit for spinal stenosis, duloxetine was interacting with oxycodone at CYP2D6. As a result, plasma concentrations of oxycodone and its active metabolite oxymorphone were likely to be higher and lower, respectively, thereby increasing the likelihood for ADEs and/or pharmacotherapy failure for oxycodone. This interaction may have contributed to the chronic constipation that the patient was experiencing [32]. Following the discontinuation of duloxetine, the competitive inhibition that was reducing

the formation of oxycodone to oxymorphone will no longer be present. Therefore, the patient should be closely monitored following this medication change, since fluctuations in serum concentrations are expected and can result in the patient experiencing enhanced pain relief, as well as ADEs (*e.g.,* respiratory depression).

The DDI perpetrated by duloxetine at CYP2D6 also impacted the patient's metoprolol. The plasma concentration of metoprolol was likely to be higher than predicted, which increases the likelihood of ADEs (*e.g.,* hypotension, bradycardia). Although the patient's pulse and blood pressure were stable, minimizing the risk of ADEs was in the best of interest of a hospice patient, who is generally more vulnerable to the detrimental effects of hypotension [6]. With the removal of duloxetine, changes in the plasma concentrations of metoprolol are expected; therefore, blood pressure should be closely monitored to maintain stability. Furthermore, the pharmacist recommended to deprescribe furosemide due to the increased risk of hypotension, dizziness, falls, and suboptimal quality of life with antihypertensives at the end of life [6]. Since the patient was normotensive (124/76 mmHg) at the time of the pharmacist's review, the healthcare team did not deprescribe metoprolol. On the other hand, furosemide was discontinued due to a subtherapeutic dosage (Table 1), lack of symptomatic edema, and the patient's frailty [33]. Although loop diuretics, such as furosemide, may be used to treat fluid overload and improve symptoms, this class of drugs can be subject to deprescribing in the hospice setting [34]. Chronic diuretic therapy may become inappropriate as physical deterioration progresses at the end of life due to increased risk of postural hypotension and electrolyte disturbances [34].

Conclusion

Maintenance of quality of life is the cornerstone of hospice care. Patients with terminal illness may have multiple comorbidities with complex medication regimens, and as their illness progresses, hospice patients are prescribed additional medications, increasing the risk of ADEs and DDIs. Pharmacists can play a unique role in deprescribing chronic medications that are no longer needed and/or could result in ADEs for a patient entering hospice care. If implemented, such recommendations have the potential to optimize patient outcomes and mitigate the risk of ADEs, while creating opportunity for optimized comfort and care in patients entering the hospice setting.

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Informed Consent Statement

Verbal informed consent was obtained.

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Conflicts of Interest

S.M., N.S.A., C.B., J.T., and V.M. are employees and shareholders of Tabula Rasa Healthcare. J.S. has no conflict of interests to declare.

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