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Pharmacist-Led Medication Review Identifies and Mitigates Fall-Risk-Increasing Drugs and Multi-Drug Interactions

Katie Pizzolato[1], Adriana Matos[1], Jacques Turgeon[2,3] and Chandni Bardolia[1]*

[1]Tabula Rasa Healthcare, Office of Translational Research and Residency Programs, Moorestown, New Jersey, USA
[2]Tabula Rasa HealthCare, Precision Pharmacotherapy Research and Development Institute, Orlando, Florida, USA
[3]Faculty of Pharmacy, Université de Montréal, Montreal, Quebec, H3T 1J4, Canada

Abstract

Purpose: Falls, a common cause of injuries and hospitalizations, are observed more commonly as age increases. Several factors may potentiate a fall including vision impairment, muscle weakness, and medications. Among those, medication use is a modifiable risk factor that pharmacists can address to lower the risk for falls and falls-related injuries. Fall-risk-increasing drugs are associated with adverse drug events such as sedation, dizziness, impaired coordination, and orthostatic hypotension. The purpose of this case report is to present mitigation strategies a clinical pharmacist provided after a medication review that identified a fall-risk-increasing drug and multi-drug interactions, to which its resultant intervention reduced the risk for falls and improved patient safety.

Case: A 63-year-old male who suffered a recent fall in his home received a targeted fall assessment medication review by a clinical pharmacist. Upon review, the clinical pharmacist identified hydroxyzine as a fall-risk-increasing drug and identified drug-drug interactions with simvastatin and fluoxetine that could increase the risk for hydroxyzine-related adverse drug events. Additionally, other fall-risk-increasing drugs (e.g., clonazepam, meclizine, fluoxetine) were present, each involved in one or more drug-drug interactions. As a first step, the clinical pharmacist recommended to discontinue the hydroxyzine to lower his risk for a future fall and fall-related injury.

Conclusion: This case demonstrates an example of a clinical pharmacist's interventions that resulted in a reduction of falls risk, along with the improvement of patient safety.

Keywords: Hydroxyzine • Simvastatin • Fluoxetine • Fall-risk-increasing drugs • Multi-drug interactions • Competitive inhibition • Cytochrome P450

Abbreviations: FRIDs: Fall-Risk-Increasing Drugs • ADE: Adverse Drug Event • CYP: Cytochrome P450 • DDI: Drug-Drug Interaction • ACB: Anticholinergic Burden • SDV: Sedative Burden • PCP: Primary Care Physician • SSRI: Selective Serotonin Reuptake Inhibitor

Introduction

Falls are a common cause of injuries and hospitalizations, and are observed more commonly as age increases [1]. Considering that several factors may potentiate a fall, mitigation strategies should be targeted towards those that are modifiable. For example, medication use is deemed a modifiable risk factor and should be addressed to lower the risk for falls and falls-related injuries [1]. When accessing medication use, it would be prudent for healthcare professionals to closely monitor for Fall-Risk-Increasing Drugs (FRIDs). FRIDs are medications that perpetuate falls due to Adverse Drug Events (ADEs), such as sedation, dizziness, impaired coordination, and orthostatic hypotension [2]. Examples of FRIDs include anticholinergics (e.g., oxybutynin), antihypertensives (e.g., amlodipine), first-generation antihistamines (e.g., diphenhydramine), and antipsychotics (e.g., quetiapine). Routine evaluation of the risks and benefits of FRIDs will help reduce the risk of falls, especially in the older adult population [3].

While studies have demonstrated the importance of identifying FRIDs within a medication regimen, their risk for falls-related ADEs can be further exacerbated by Drug-Drug Interactions (DDIs) [2]. Specifically, pharmacokinetic DDIs involving inhibition or competitive inhibition result in increased plasma concentration of the victim medication, thus increasing the risk for ADEs [4,5]. Clinical pharmacists are well-equipped to identify DDIs due to their ability to incorporate pharmacokinetic and pharmacodynamic concepts into their medication reviews. Combining implementation of clinical pharmacist recommendations with the expertise of a healthcare team results in enhanced medication safety for the patient [6]. This case report will present an example of a clinical pharmacist-led medication review that resulted in the identification and mitigation of a FRID and DDIs, which ultimately lowered the risk of recurrent falls for a patient.

Case Presentation

A 63-year-old male with a MedWise™ Risk Score of 35, Aggregated Anticholinergic Burden (ACB) estimated as HIGH, Aggregated Sedative Burden (SDV) estimated as VERY HIGH and an extensive past medical history (Table 1) reported to his Primary Care Physician (PCP) and medical team for assessment due to a recent fall in his home. The patient reported feeling drowsy while transferring himself in the restroom during a nighttime awakening, which caused him to lose his balance. Considering that the patient had a history of recurrent falls, the PCP asked a clinical pharmacist to complete a targeted fall assessment medication review to determine if the cause could be medication-related. Upon review of the patient's complex medication regimen (Table 1), the clinical pharmacist identified one of the bedtime medications, hydroxyzine, as a FRID. The patient was prescribed hydroxyzine to manage his anxiety. Additionally, the clinical pharmacist noted that the patient was prescribed simvastatin at bedtime, which has a stronger affinity for the cytochrome P450 (CYP) 3A4 enzyme than hydroxyzine (Figure 1). The patient was also prescribed fluoxetine, which has a stronger affinity for the CYP2D6 enzyme than hydroxyzine. When co-administered, simvastatin and fluoxetine are expected to competitively inhibit the metabolism of hydroxyzine

***Address for Correspondence:** Bardolia C, Tabula Rasa Healthcare, Office of Translational Research and Residency Programs, Moorestown, New Jersey, USA, E-mail: cbardolia@trhc.com*

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Table 1. Current medical history and medication list.

Conditions	Medication	Dose	Frequency
Amyotrophic lateral sclerosis	Riluzole	50 mg	Every 12 hours
Anxiety	Hydroxyzine	50 mg	Once at bedtime
	Clonazepam	1 mg	Once at bedtime
	Clonazepam	0.5 mg	Once daily as needed
Benign Prostate Hyperplasia	Tamsulosin	0.4 mg	Once every evening
Chronic pain	Pregabalin	50 mg	Three times daily
	Ibuprofen	400 mg	Every 6 hours as needed
	Acetaminophen	325 mg	1-2 tablets every 6 hours as needed
Circulation	Aspirin	81 mg	Once every morning
Constipation	Docusate	100 mg	Twice daily as needed
Dizziness	Meclizine	25 mg	Three times daily as needed
Hypercholesterolemia	Simvastatin	40 mg	Once at bedtime
Major Depressive Disorder	Fluoxetine	20 mg	Once every morning
Nausea	Ondansetron	4 mg	Every 8 hours as needed
Parkinson's disease	Carbidopa/levodopa	25/250 mg	Four times daily
Restless leg syndrome	Ropinirole	1 mg	Three times daily
Vitamin D deficiency	Cholecalciferol	2000 units	Once every morning

on CYP3A4 and CYP2D6, respectively. These interactions result in higher concentration of hydroxyzine, and this which further increases the patient's risk for hydroxyzine-related ADEs, including falls. Other FRIDs (i.e., meclizine, fluoxetine, clonazepam) were also present in the patient's medication regimen, all of which were part of one or more DDIs involving competitive inhibition that resulted in increased concentrations of meclizine or clonazepam. These interactions further increased the patient's risk for a fall and were to be considered subsequently in future assessments.

Considering the highly sedative and anticholinergic effects of hydroxyzine, as well as the DDIs with simvastatin and fluoxetine, the clinical pharmacist recommended discontinuation of therapy. The recommendation was accepted by the PCP and this implemented recommendation reduced the patient's exposure to FRIDs. Upon follow-up three months later, the patient's anxiety was controlled without utilization of hydroxyzine. Furthermore, the patient's medical team was able to continue to reduce his exposure to FRIDs and DDIs by discontinuing his fluoxetine, his meclizine, and his as-needed prescription for clonazepam.

Discussion

Hydroxyzine is a first-generation antihistamine that acts as an inverse agonist of histamine H1-receptors and is able to penetrate the blood-brain barrier [7]. Hydroxyzine is unique compared to other first-generation antihistamines (e.g., diphenhydramine) because it exhibits an effect on serotonin type-2A (5-HT2A) receptors, making it the only antihistamine approved for the management of anxiety [7]. Due to its actions in the brain, hydroxyzine can cause sedation, drowsiness, and fatigue, all of which are associated with an increased risk for falls [1]. Additionally, hydroxyzine blocks the neurotransmitter acetylcholine, resulting in anticholinergic side effects such as confusion, dry mouth, and constipation [4]. Medications with highly anticholinergic properties should be used with caution in older adults, since utilization of these medications long-term may increase the risk of cognitive decline, including dementia [8].

Considering the highly sedative properties of hydroxyzine, it is often prescribed at bedtime to aid in sleep and to avoid daytime drowsiness. Since hydroxyzine utilizes the CYP3A4 and CYP2D6 enzymes for its metabolism, there is a possibility for DDIs with medications that utilize the same pathways [9,10]. Hydroxyzine is a weak-affinity substrate for both CYP enzymes, utilizing CYP3A4 as its major pathway for metabolism compared to CYP2D6 [9,10]. Simvastatin is a common cholesterol-lowering medication, which acts as a moderate-affinity substrate for CYP3A4 [11]. When administered concomitantly, simvastatin exhibits competitive inhibition at CYP3A4.

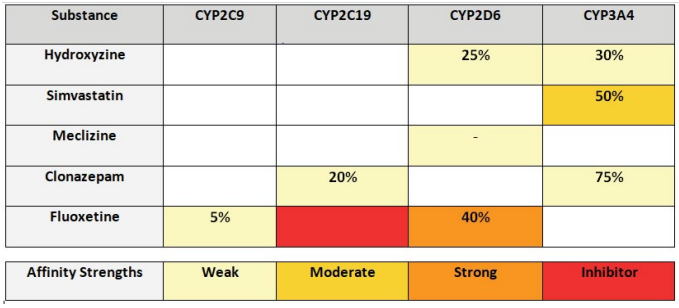

Figure 1. Summary of affinity and cytochrome P450 (CYP450) metabolic pathways.

Simvastatin will bind more strongly to CYP3A4 displacing hydroxyzine, which results in increased concentration of hydroxyzine [9,10]. In addition, fluoxetine, a Selective Serotonin Reuptake Inhibitor (SSRI) which is also prescribed for this patient, acts as a strong-affinity substrate for CYP2D6 enzyme, as well as an inhibitor of CYP2C19 enzyme [12]. Both fluoxetine and its active metabolite, norfluoxetine, demonstrate prolonged inhibitory effects by means of competitive inhibition on the CYP2D6 enzyme [12]; therefore, when hydroxyzine, a CYP2D6 moderate-affinity substrate, and fluoxetine are both utilized in a medication regimen, regardless of time of administration, competitive inhibition will occur at CYP2D6 and result in increased concentrations of hydroxyzine [9,12]. These DDIs result in an increased risk for hydroxyzine-related ADEs, such as sedation, and further increases the risk for a medication-related fall.

Though the clinical pharmacist only recommended the discontinuation of one FRID, hydroxyzine, there were other FRIDs on this patient's medication list (i.e., clonazepam, meclizine, fluoxetine), along with several DDIs (Figure 1). Meclizine has similar anticholinergic and sedative properties as hydroxyzine and acts as a CYP2D6 weak-affinity substrate [13]. When used in combination with fluoxetine, competitive inhibition will occur at CYP2D6 and cause meclizine concentrations to increase, thus increasing the risk for meclizine-related ADEs (e.g., confusion, dry mouth, sedation) [12,13]. Additionally, clonazepam was the victim of DDIs, perpetrated by simvastatin and fluoxetine. Clonazepam is primarily metabolized by the CYP3A4 enzyme and acts as a weak-affinity substrate for both CYP3A4 and CYP2C19 [14]. When administered with simvastatin and fluoxetine, competitive inhibition at CYP3A4 and irreversible inhibition at CYP2C19, respectively, is expected to occur [11,12]. These multiple DDIs result in increased concentrations of clonazepam, further increasing the risk for clonazepam-related ADEs (e.g., sedation) [11,12,14].

While several other recommendations and interventions could have

been made for this patient, as a general principle, medication changes must be made over time, especially when adjusting medications that affect mood [15]. Of the FRIDs identified, hydroxyzine exhibited the highest sedative and anticholinergic properties and was deemed a high priority to address. Evidence from studies regarding the effects of FRIDs supports reassessing the need for these medications, and discontinuing them, if clinically appropriate [1-3]. Additionally, the American Geriatrics Society Beers Criteria® provides a strong recommendation to avoid the use of hydroxyzine and any other first-generation antihistamines due to the increased risk of falls [16]. If hydroxyzine was deemed a necessary medication for this patient, the clinical pharmacist did provide an alternative recommendation: change simvastatin to another statin medication that does not utilize CYP enzymes for metabolism or that is minimally metabolized by CYP enzymes to avoid competitive inhibition. While recommending to separate the time of administration between hydroxyzine and simvastatin could also mitigate this DDI, it is recommended to administer simvastatin in the evening [11].

Other studies have identified the importance of medication-related fall assessments for older adults. One study in particular that evaluated patients who had experienced a fall demonstrated that calculated fall risk levels from elderly fall assessments may be underestimated due to the lack of consideration for a patient's medication regimen [2]. While some patients' fall risk levels may be falsely low, the patients with higher level fall risks without incorporation of their medications were also commonly prescribed FRIDs [2]; therefore, this study concluded that conducting a medication-related fall assessment can provide benefit in the elderly population by routinely reviewing medications linked to falls [2]. Additionally, a recent study aimed to evaluate the impact of pharmacist-led interventions on the recurrence of falls in the elderly [17]. Pharmacists completed medication reviews for patients who had previously experienced a fall, assessing for FRIDs, ADEs and DDIs, and made recommendations in order to reduce future fall risk. Of the total recommendations to reduce fall risk, 80 percent were accepted and implemented by health care providers; furthermore, a significant 12.4 percent reduction (p=0.033) was observed in recurrent falls after the pharmacist-led interventions [17]. This study further demonstrated the importance of incorporating pharmacist interventions, as they were highly accepted by health care providers and were associated with a significant reduction in recurrent falls [17].

Conclusion

A clinical pharmacist-led fall assessment review resulted in the discontinuation of a FRID, hydroxyzine, in a patient with frequent falls. In addition to lowering fall risk, the clinical pharmacist identified DDIs that may have further increased the patient's fall risk. Incorporating a clinical pharmacist as part of an interdisciplinary healthcare team enables identification of FRIDs, and promotes optimized medication regimens to provide improved quality of care to a patient.

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