

Improper administration

Silent culprit of drug therapy problems

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Proper timing of medication administration can maximize effectiveness, minimize adverse effects, optimize adherence, and prevent unnecessary polypharmacy. This is because drug-food interactions and medication temporal patterns can have substantial effects on patient outcomes. This article examines some commonly used medications that are prone to improper administration and outlines solutions for addressing these challenges. Consideration should also be given to clinical judgment, consistency, and individualization of drug therapy to patient and caregiver needs beyond the general recommendations found in this article.

Case presentation

Anna, a frail 81-year-old woman, is new to your practice after another family doctor in your area retired. Anna has multiple medical conditions including hypertension, nonvalvular atrial fibrillation (for about 1 year), diabetes, hypothyroidism, and osteoporosis. She was diagnosed with Alzheimer disease by your colleague approximately 1 year ago and began treatment for iron deficiency anemia 3 months ago. Anna also has a long list of medications (Table 1).

At Anna's second appointment with you she is accompanied by her daughter Jane. Anna lives with Jane and relies on her for assistance with instrumental activities of daily living, as well as bathing and dressing. They would prefer that Anna continue living at home for as long as she can. Jane manages Anna's medications by filling a dosette box for her and reminding her to take them, proudly stating that Anna "never misses a dose." However, Jane has some concerns about Anna's health: she is often tired during the day but wanders in the night, and she has pedal edema, which makes wearing shoes uncomfortable. Anna previously wore compression stockings but has been resistant to this lately because donning them is difficult.

During Anna's last appointment (1 month ago), you decided not to make changes to her medications but sent her for bloodwork. You also requested that her pharmacy perform a full medication review, including details on the time of day that medications are given, administration with food, and any over-the-counter medications not on your file. Table 1 and Box 1 show her current medication regimen, bloodwork, and vital signs. As you review her medications, you identify several potential issues.

Timing medications with food

Some medications have increased absorption and effectiveness when taken with food (eg, nitrofurantoin,¹ metformin extended release [XR],² and rivaroxaban doses ≥ 15 mg).^{3,4} Food can also be a useful tool for improving tolerability and reducing the gastrointestinal side effects of many drugs (including metformin, prednisone, iron supplements, and nonsteroidal anti-inflammatory drugs).^{5,6} However, some medications have substantially decreased absorption in the presence of food (eg, bisphosphonates,⁷ levothyroxine,⁸ iron supplements,⁹ and cloxacillin¹⁰), which reduces clinical effect. Table 2 describes the change in bioavailability (extent of absorption) among selected medications when taken with food compared with an empty stomach.^{7,11-32}

Anna is taking several medications that are time sensitive with regard to meals. Her metformin XR is both better absorbed (increases by 50%) and better tolerated if taken with food.^{17,18} Her dose of rivaroxaban is recommended by guidelines³³ and product manufacturers³ to be taken with a meal to increase bioavailability (from

Table 1. Anna's detailed medication history

MEDICATION	TIME TAKEN	INITIATION
Alendronate, 70 mg weekly	Sunday mornings at 8:00 AM with a small breakfast	7 mo ago
Amlodipine, 10 mg daily	8:00 AM at breakfast	NA
Atorvastatin, 20 mg daily	8:00 AM at breakfast	NA
Levothyroxine, 125 µg daily	8:00 AM at breakfast	NA
Rivaroxaban, 20 mg daily	Bedtime (without food)	10 mo ago (switched from warfarin)
50 mg sitagliptin and 1000 mg metformin XR, 2 tablets once daily	8:00 AM at breakfast	3 mo ago (switched from metformin IR)
Metoprolol, 25 mg twice daily	8:00 AM at breakfast and supper	NA
Donepezil, 10 mg daily	Bedtime	1 y ago
Calcium carbonate, 500 mg daily	8:00 AM at breakfast	NA
Vitamin D, 1000 units daily	8:00 AM at breakfast	NA

IR—immediate release, NA—not available, XR—extended release.

66% to 80% up to 100%) and thus avoid inadequate anti-coagulation that may occur under fasting conditions (note that rivaroxaban doses of ≤ 10 mg have high absorption regardless of food intake).¹⁹⁻²¹ Her weekly alendronate should not be taken with breakfast since this decreases absorption by 85% to 90%, rendering it ineffective.^{7,11} Only bisphosphonates that are delayed release (DR) can be taken after food (eg, risedronate DR).³⁴ Although Anna's levothyroxine has reduced bioavailability when taken with food (decreased by about 15%),^{8,16,35} the dose can be titrated to target thyroid-stimulating hormone (TSH) and thyroxine (T_4) levels. Thus, consistency with levothyroxine administration is most important. In this case, because Anna's TSH and T_4 levels are within normal limits, the timing of levothyroxine does not necessarily have to be changed.

In summary, it is important that Anna take her metformin XR-sitagliptin combination and rivaroxaban with sizable meals; her alendronate with a glass of water and without food or other medications; and her levothyroxine consistently either with or without food.

Box 1. Anna's medical history

Recent bloodwork

Results

- eGFR=69 mL/min
- Serum creatinine=71 μ mol/L

Levels within normal limits

- TSH=0.87 mIU/L
- T_4 =16 pmol/L
- Electrolytes
- Calcium
- Lipid panel

Abnormal levels

- Increased HbA_{1c} =8.4% (3 mo ago=8.9%)
- Decreased Hb=103 g/L
- Decreased iron=5.4 μ mol/L
- Decreased TIBC=49 μ mol/L
- Decreased TSAT=11%
- Decreased ferritin=13 μ g/L
- Decreased MCV=76.8 fL

Physical examination

Findings on presentation

- Blood pressure=132/84 mm Hg
- Heart rate=74 beats/min
- No shortness of breath
- 2+ pitting edema
- MMSE=20/30 (vs 23 upon dementia diagnosis)

Previous chart history findings

- Echocardiogram 2 y ago, LVEF=59%
- Intolerance to sulfonylureas

eGFR—estimated glomerular filtration rate, Hb—hemoglobin, HbA_{1c} —hemoglobin A_{1c} , LVEF—left ventricular ejection fraction, MCV—mean corpuscular volume, MMSE—Mini-Mental State Examination, T_4 —thyroxine, TIBC—total iron bonding capacity, TSAT—transferrin saturation, TSH—thyroid-stimulating hormone.

Important drug-mineral interactions

Chelating medications must be properly spaced from minerals. When polyvalent cations (calcium, magnesium, aluminum, or iron) are administered with certain drugs (such as ciprofloxacin or tetracycline), the formation of an insoluble “chelate” complex can prevent absorption.^{36,37} **Table 3** lists some common chelating medications and how to time their administration (typically about 2 hours before or roughly 4 hours after minerals).^{7,35,38-44} Of note, many polyvalent cations are found in food (eg, calcium in milk) and in over-the-counter products (eg, multivitamins, antacids), which can inadvertently create drug interactions. Minerals can also negatively affect each other: for example, calcium can reduce iron absorption.^{25,45} Switching calcium supplements to dietary sources while decreasing product interactions may be preferred by guidelines (as long as dairy is not taken with chelating medications).⁴⁶ Since chelation and intestinal interactions can drastically decrease bioavailability—sometimes by more than 90%—identification of these problems and subsequent separation is necessary to maximize effectiveness.⁴⁷

Anna has prescriptions for 2 chelating medications (levothyroxine and alendronate) and 1 polyvalent cation (calcium carbonate). Anna will not adequately absorb her alendronate if it is not spaced apart from her calcium supplement as well as dietary interactions. Her levothyroxine does not necessarily require separation if her thyroid test results remain stable.

Medications at the optimal time of day

Chronotherapeutics refers to timing medical treatment based on circadian rhythms to increase the effectiveness of medications or to minimize adverse effects.^{48,49} Evidence in this field of medicine is emerging but sometimes conflicting.

Dihydropyridine calcium channel blockers. These, such as amlodipine and nifedipine, can induce pedal edema. Strategies to minimize this side effect include lowering the dose, switching to a different drug, combining with an angiotensin-converting enzyme inhibitor,⁵⁰ or administering at bedtime. A randomized study involving nifedipine XR showed edema rates of 13.4% when nifedipine was administered in the morning compared with 1% in the evening.⁵¹ Since leg elevation (eg, lying with a pillow under the legs) can reduce edema by shifting fluid back to the heart,^{52,53} timing peak drug levels at night may lessen daytime symptoms. Chronotherapeutic studies have yet to be conducted on other dihydropyridine calcium channel blockers in this context.

Stimulating medications. These medications, such as bupropion, methylphenidate, and steroids, are best taken in the morning to prevent sleep disturbances,

Table 2. Bioavailability of common medications when taken with or without food

MEDICATION	ADMINISTRATION		OTHER ABSORPTION INTERACTIONS	COMMENTS
	EMPTY STOMACH (NO FOOD OR MEDICATIONS)	WITH OR AFTER FOOD		
Alendronate	Recommend on empty stomach	Decreases absorption by 85%-94% ^{7,11,12}	Calcium and cations,* coffee or orange juice (decreases alendronate by 40%), ¹¹ proton pump inhibitors	Bioavailability for most bisphosphonates is negligible when taken with food. However, the efficacy of risedronate DR is preserved when taken with food ^{7,13}
Risedronate IR	Recommend on empty stomach			
Risedronate DR	Increased risk of adverse effects (eg, abdominal pain)	Recommend with or after food ^{14,15}		
Levothyroxine	Recommend on empty stomach	Decreases absorption by 15% (can be taken consistently with food)	Coffee, soy, cations	Food slightly decreases absorption, but dose can be titrated to target TSH levels if taken consistently ¹⁶
Metformin XR	Decreases absorption by about 50%	Recommend with or after food	NA	Metformin XR requires a substantial meal for adequate absorption ^{17,18}
Rivaroxaban, ≥15 mg	Decreases absorption by 20%-30%	Recommend with or after food	NA	Taking ≥15 mg rivaroxaban on an empty stomach may result in inadequate anticoagulation ¹⁹⁻²¹
Rivaroxaban, ≤10 mg	May be taken with or without food			
Iron (oral tablets)	Empty stomach has best absorption, but worse tolerability (eg, increases gastrointestinal adverse effects by 4%-43%) ²²	With food has best tolerability, but worse absorption (eg, lowers absorption by about 40%-60%) ^{23,24} Note: pairing iron tablets with rice meals showed higher absorption (increases 40%) than with other meals ²⁴	Calcium, phytic acids, polyphenols, animal or soy proteins ²⁵ Taking with vitamin C to boost absorption is controversial: in 1 study, adding vitamin C to ferrous succinate did not meaningfully affect hemoglobin levels. ²⁶ However, plant-based (ferric) dietary sources of iron may receive an absorption boost from vitamin C ^{27,28}	Food, low acidity, and cations can impair iron absorption. ²⁵ Bioavailability can be increased with higher doses, by alternating day dosing, ²⁸⁻³⁰ or when taken on an empty stomach (if tolerated) Note: the absorption and tolerability of iron varies depending on formulation
Nitrofurantoin	Decreases absorption by 30%-80% ³¹	Recommend with or after food	NA	Food maximizes absorption and effect
Cloxacillin	Recommend on empty stomach	Peak concentration decreases by >50% ³²	NA	Food can decrease effectiveness

DR—delayed release, IR—immediate release, NA—not applicable, TSH—thyroid-stimulating hormone, XR—extended release.

*Cations include calcium, magnesium, aluminum, and iron.

while sedating medications (such as fluvoxamine, amitriptyline, and olanzapine) should be taken in the evening to avoid daytime drowsiness.^{54,55,56} Although originally recommended by the manufacturer to be taken in the evening,⁵⁷ donepezil can be taken in the morning.⁵⁸ A small trial of 54 patients taking donepezil showed that those who were randomized to take

donepezil in the evening had worse sleep outcomes than those in the morning group.⁵⁹

Antihypertensive medications. The timing of antihypertensive medications is contentious. Evidence from clinical trials showed absolute risk reductions in cardiovascular events of 11% and 5.4%, respectively, when

Table 3. Chelating medications and cation administration times: Cations include calcium, magnesium, aluminum, and iron.

MEDICATION	ADMINISTRATION SPACING		EXCEPTIONS
	TAKE BEFORE CATION	TAKE AFTER CATION	
Bisphosphonates (risedronate, alendronate, etidronate) ⁷	30 min to 2 h (earlier is better)	30 min to 2 h (later is better)	NA
Thyroid medications (levothyroxine, desiccated thyroid) ^{35,38}	Ideally 4 h (some studies 2 h)	Ideally 4 h (some studies 2 h)	NA
Fluoroquinolone antibiotics ³⁹			
• Ciprofloxacin	2 h	6 h	NA
• Moxifloxacin	4 h	8 h	Calcium
• Levofloxacin, delafloxacin	2 h	2 h	NA
Tetracycline antibiotics (doxycycline, minocycline, tetracycline) ^{40,41}	2 h	3-4 h	Doxycycline and minocycline may be taken with milk or food. Take tetracycline 1 h before or 2 h after food or milk ⁴²
HIV medications—INSTIs ^{43,44}			Recommendations vary among products depending on ion and whether food is taken with the ion and medication
• Bictegravir	2 h	4 h	
• Dolutegravir	2 h	6 h	
• Elvitegravir	2 h	2-4 h	
• Raltegravir	Cations not recommended	Cations not recommended	

INSTI—integrase strand transfer inhibitor, NA—not applicable.

antihypertensives were taken at bedtime compared with the morning.^{60,61} However, methodologic issues make this evidence uncertain.⁶² More recently, a 5-year study revealed no difference in risk of cardiovascular events between bedtime and morning administration (3.4% vs 3.7%, hazard ratio=0.95).⁶³ Upcoming results of a Canadian trial will shed additional light on the subject.⁶⁴ Prioritizing adherence by giving antihypertensives at the most convenient time of day for patients is likely best.

Statins. Statins are conventionally taken at bedtime since cholesterol synthesis peaks then, but this is not always required. Long-acting statins (atorvastatin, rosuvastatin, and fluvastatin XR) can be taken at any time of day without consequence. Short-acting statins (fluvastatin, lovastatin, pravastatin, and simvastatin) have half-lives of 6 hours or less and may be best taken at night for maximum low-density lipoprotein reduction.^{65,66} Of note, hard outcomes such as cardiovascular events and mortality have not yet been examined in relation to timing.

Anna's donepezil can be stimulating and is best taken in the morning to minimize sleep disturbances. Her amlodipine could be trialed at bedtime to see if this reduces her leg swelling and increases the antihypertensive effect, although data to support this approach are limited. Evidence suggests Anna's atorvastatin can be

taken at any time of day (although if she were taking a short-acting agent such as simvastatin, bedtime administration might be best).

Case resolution

After analyzing Anna's bloodwork, evaluating medication administration patterns, and consulting with Jane and Anna, you recommend the following:

- Switch donepezil from evening to morning administration to attempt to improve Anna's sleep.
- Have Anna take her weekly alendronate as soon as she wakes up, with plain water, at least 30 minutes before breakfast and other medications to maximize absorption. Alternatively, a switch could be made to risedronate DR to allow for administration with a meal and other medications, but this formulation is not covered by government drug benefit plans in most Canadian provinces and may cost Anna about \$15 more per month.
- Move rivaroxaban administration from bedtime to suppertime (her largest meal) to maximize absorption and thus maximize stroke prevention.
- Move Anna's metformin XR and sitagliptin to suppertime (her largest meal) to maximize absorption.
- Administer amlodipine at supper in the hope of improving her pedal edema. Alternatively, adding an


angiotensin-converting enzyme inhibitor or angiotensin receptor blocker might help.⁵⁰

- Move calcium carbonate to suppertime to avoid interactions with alendronate and levothyroxine. Alternatively, consideration may be given to stopping Anna's calcium supplement and encouraging dietary calcium sources (which would still require spacing from alendronate and levothyroxine).
- Continue levothyroxine at breakfast, since Anna's thyroid function test results are within range. However, you reorder thyroid function tests for 6 weeks from now, since you suspect Anna's levothyroxine dose may have to be adjusted after removal of the calcium drug interaction.

Since you are substantially changing Anna's medication routine, you also recommend that her pharmacy place her medications in blister packs.

Conclusion

Hidden interactions—both helpful and harmful—can impact drug absorption, so it is important to properly space medications to avoid interference from chelates and to note when administration with or without food may be necessary. Similarly, taking medications at the wrong time of day can result in unwanted side effects or hinder therapeutic effect. When managing medical conditions that can be reactively dose adjusted based on laboratory results (eg, TSH and T₄ levels, international normalized ratio, and cholesterol levels), consistency in medication administration is usually the top priority. However, optimal administration time is most essential when the effectiveness of medications, like bisphosphonates, cannot be readily monitored. By analyzing an existing medication regimen before adding new drugs, the harms associated with polypharmacy and prescribing cascades can be reduced.

In Anna's case, her medication schedule changed to 3 times per day. This type of schedule may not be manageable for every patient. When caregiver support for "perfect" medication timing is limited, alternative medications may need to be chosen (or new therapeutic goals set). Providers can find the balance between optimal medication timing and a schedule that works for patients and caregivers. 

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