

Pharmacotherapy for the Elderly Dental Patient

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ABSTRACT

Current demographic data clearly show that the North American population is aging, and projections suggest that the percentage of older people will increase. The elderly often suffer from multiple chronic conditions that affect their quality of life, use of health services, morbidity and mortality. Also, in those of advanced age, the pharmacokinetics and pharmacodynamics of many drugs are altered. Polypharmacy increases the incidence of adverse drug reactions and drug interactions in this population. Thus, the dentist must be continually aware of the pharmacologic status of each patient and consider the likelihood of interactions between drugs prescribed by the dentist, drugs prescribed by the physician and drugs that are self-administered, including over-the-counter medications and natural supplements. In this article, we discuss pharmacokinetic and pharmacodynamic changes in the elderly patient, polypharmacy and the changes in prescribing for our dental patients. Specific emphasis is placed on the drugs commonly prescribed by dentists: local anesthetics, analgesics and antibiotics.

Epidemiology

The world population of those age 65 years and older has increased rapidly in the last century, and a further increase is expected.¹ Currently, about 15% of North Americans are over 65 years of age. By 2030, this age group will make up 25% of the population. People 85 years of age and over constitute the fastest growing segment of the North American population, and their numbers are increasing at an average rate of 5% a year.^{2,3} Elderly people are prescribed the highest proportion of medications, and, by 2040, the elder population is expected to consume 40% of all prescriptions used.⁴ Pharmacotherapy is the single most important intervention for care of most elderly patients.⁵ **Table 1** lists the drugs most widely prescribed for the elderly population.⁶

Table 1: Drugs most commonly prescribed to elderly patients in the United States.

Indications	Drugs
Analgesia	Hydrocodone, acetaminophen, ibuprofen
Hypercholesterolemia	Rosuvastatin, atorvastatin, simvastatin
Hypertension	Lisinopril, atenolol, metoprolol
Endocrine dysfunction	Levothyroxine, metformin
Infection	Amoxicillin, azithromycin
Prevention of blood clotting	Clopidogrel, warfarin
Depression	Escitalopram, trazodone
Gastroesophageal reflux disease and acid reflux	Esomeprazole
Respiratory problems	Montelukast, salbutamol

Normal Physiological Changes with Aging

The aging process includes 3 types of physiological changes⁷: changes in cellular homeostatic mechanisms, which may include regulation of body temperature, as well as blood and extracellular fluid volumes; those related to a decrease in organ mass; and those involving a decline in, and loss of, the functional reserves of the body's systems⁷ (**Table 2**).

Table 2: Normal physiological changes in elderly patients.

System	Change with age
Central nervous system	↓ neuronal density
	↓ reflexes
	↓ sympathetic response
Cardiovascular system	↓ cardiac output
	↓ baroreceptor activity
	↑ total peripheral resistance
Gastrointestinal system	↓ gastric emptying
	↓ gastrointestinal motility
	↑ gastric pH
	↓ intestinal blood flow
Respiratory system	↓ tidal volume
	↓ vital capacity
	↑ residual volume
	↓ lung capacity
Renal system	↓ renal blood flow
	↓ glomerular filtration
	↓ tubular secretion
Immune system	↓ neurohumoral response
	↓ white blood cells
	↓ cell-mediated immunity

Sources: Reddy et al. (2012)⁵ and Nigam et al. (2012).⁷

Pharmacokinetics

The term pharmacokinetics is used to describe the disposition of a drug after its administration, specifically, its absorption, distribution, biotransformation and elimination. Alterations in these parameters in the elderly most often result from age-related decline in certain physiological functions, such as decreased cardiac output, decreased renal function or decreased plasma albumin concentrations.⁸

Absorption — When a medication is taken orally, the drug must be absorbed from the gastrointestinal tract into the blood stream. A number of changes that occur during the aging process may alter this process: increased gastric pH, decreased gastric emptying, decreased gastrointestinal blood flow and impaired motility have been reported.^{9,10} Increased gastric pH and reduced gastric blood flow may reduce drug absorption, whereas lower gastrointestinal motility may result in more of the drug being absorbed. Concurrent use of antacids and overuse of commonly prescribed proton pump inhibitors may contribute greatly to these changes.^{11,12} Although gastrointestinal function decreases with age, most studies of drug absorption have demonstrated minimal effects. Nevertheless, other underlying conditions in elderly patients, such as swallowing difficulties, poor nutrition, erratic meal

patterns, multiple gastrointestinal conditions and dependence on feeding tubes, may affect absorption of many drugs.^{9,11}

Distribution — After a drug is absorbed and enters the bloodstream, it is distributed to various organs and tissues throughout the body. Changes in body composition of geriatric patients may influence drug distribution. Aging is associated with a decrease in total body water and lean body mass and an increase in fat tissue stores.^{5,9} As a result, the volume available for distribution of water-soluble drugs is smaller, resulting in a higher plasma concentration for a given dose and the increased likelihood of a more profound effect or possible toxic reaction. Moreover, aging is associated with a decrease in plasma albumin; this may be significant for a patient taking acidic drugs, which are normally highly bound to this protein. As serum albumin concentration decreases, the fraction of free or unbound drug increases. This will result in a larger volume of distribution because more of the drug is free to spread to the rest of the body, possibly enhancing its pharmacological action.

Biotransformation — The main organ involved in biotransformation (or metabolism) is the liver. For most drugs, metabolism occurs in 2 phases. Phase I reactions involve formation of a new or modified functional group or cleavage through oxidation, reduction or hydrolysis. Phase II reactions involve conjugation to enhance elimination. The physiological changes of aging also affect drug metabolism.¹¹ Hepatic blood flow is reduced and, thus, the drug is introduced to the liver at a much lower rate.¹¹ Liver mass and intrinsic metabolic activity, including the CYP450 enzyme system, which is the primary means of drug biotransformation, are also reduced during aging.¹¹ Phase I reactions are affected much more than phase II reactions. With reductions in blood flow to the liver and in metabolic activity, the metabolic process is significantly reduced in geriatric patients.^{11,13,14} Furthermore, chronic diseases, such as hepatitis and cirrhosis, that damage the hepatocytes can further complicate the ability of the liver to metabolize medications properly.¹⁵ Slower metabolism and decreased clearance rate can lead to accumulation of the medication in the plasma, increasing its concentration and predisposing to toxicity.

Elimination — Although drugs and foreign substances are eliminated from the body by a number of routes, the major organ involved in excretion is the kidney. Kidney function declines with increasing age; a decrease in kidney mass and a reduction in functional nephrons have been reported.^{5,9} Moreover, in the elderly, mean glomerular filtration rate and renal plasma flow are reduced 30% compared with the young.^{9,10} Taken together, these factors impair elimination of drugs from the body and can lead to an increase in effects and toxicity. Reduction of doses may be required to reduce the likelihood of adverse effects.

The overall impact of these pharmacokinetic changes in the elderly is to increase the duration of a drug's action and its plasma concentration, with the latter leading to increased potency.

Pharmacodynamics

Pharmacodynamics refers to the action of a drug on the body, which may be affected by physiological changes in organ function related to aging or specific disease processes. Pharmacodynamics are particularly important for drugs that affect the central nervous system (CNS) and the cardiovascular system. In this regard, as the body ages, the affinity of some medications for particular receptor sites may change.¹¹ The number of receptor sites may also change over time, thus affecting the efficacy of some drugs.^{11,14,16}

For instance, older adults frequently show an exaggerated response to CNS drugs.¹⁷ This is partly a result of an underlying age-related decline in CNS function and partly a result of increased sensitivity to certain benzodiazepines, general anesthetics and opioids.^{9,17} Acetylcholine neurotransmission may also be affected,^{18,19} such that drugs with anticholinergic action may cause CNS effects more often in the elderly. Anticholinergic drugs may induce or increase delirium in elderly patients.^{19,20}

For cardiovascular agents, the most notable age-related pharmacodynamic difference is a decrease in the effect of beta-adrenergic agents,^{17,21} for example on heart rate and stroke volume. For most other cardiovascular drugs, the elderly have a higher risk of adverse events. Orthostatic hypotension is common, for example, as a result of decreased arterial compliance and baroreceptor reflex response in older people.^{9,22,23} Other medications, such as antipsychotic drugs and drugs for Parkinson's disease, may also cause orthostatic hypotension.

The fact that the elderly are very susceptible to CNS drugs has implications for sedation in dentistry. The action of sedatives may be more profound and prolonged among these patients; thus, side effects are more prominent and post-operative care is a concern. As for any patient, only dentists with training in sedation techniques should consider sedation for the elderly. Oral sedation should be used with great caution as it carries increased risks for the elderly compared with younger adults, and doses must be reduced significantly.

Polypharmacy, Adverse Drug Reactions and Drug Interactions

The prescription and use of multiple drugs to deal with concomitant multiple diseases is known as polypharmacy.²⁴ Numerous studies have shown that the elderly take more prescription and over-the-counter (OTC) medications than younger adults.²⁵ The most commonly used classes of OTC medications include analgesics, laxatives, vitamins and minerals. At any given time, an

elderly patient takes, on average, 4 or 5 prescription drugs and 2 or 3 OTC medications.^{24,25}

Herbal supplements have long been used by older people as a substitute for high-cost prescription medications as well as because of their overall popularity. The unmonitored use of herbal supplements can be a serious risk in this population, who are commonly given prescription medications to control multiple disorders.²⁶ For instance, many herbal preparations, such as ginkgo, ginseng, garlic and ginger, have anti-platelet and anticoagulation properties and, thus, may potentiate the effects of other anticoagulation drugs, such as warfarin. Synergistic interactions may also occur between herbal medicines and other anti-platelets drugs, such as ASA and nonsteroidal anti-inflammatory drugs (NSAIDs). Thus, geriatric patients who take warfarin and other anti-platelet medications should be advised about these interactions with herbal products.

The high prevalence of polypharmacy among the elderly may lead to inappropriate drug use, medication errors, drug interactions and adverse drug reactions. Adverse drug reactions and drug interactions are common reasons for admission to hospital of older people, are common in elderly patients in hospital and are an important cause of morbidity and mortality.²⁷⁻²⁹ The incidence of adverse drug reactions in the elderly is 3–4 times that seen in young adults. The medications most often associated with adverse reactions and interactions are anticoagulants, anticonvulsants and cardiovascular agents.²⁹ The most consistent risk factor for adverse drug reactions is number of drugs being taken, i.e., the risk rises exponentially as the number of drugs increases.⁵ Other factors that contribute to the incidence of adverse drug reactions are changes in pharmacokinetics and pharmacodynamics and comorbidities associated with the elderly patient. The symptoms of adverse drug reactions may be harder to detect in the elderly and may be misinterpreted as symptoms of a disease or even "normal aging."⁹

Although polypharmacy is acceptable in many cases of multiple comorbidities, prescribers must consider older adults' physiology.³⁰ For instance, many elderly patients are prescribed warfarin concurrently with an NSAID, a selective serotonin reuptake inhibitor (SSRI) or a lipid-lowering agent,³⁰ which may increase the risk of bleeding (already increased by use of warfarin alone).

To avoid adverse drug reactions and drug interactions, the dentist should regularly review the patient's medical history and medication list and carefully assess the need for and consequences of pharmacologic intervention. Finally, close monitoring and thorough evaluation of pharmacotherapy is important in preventing adverse drug reactions and drug interactions.^{9,19}

Changes in Prescription of Drugs Commonly Used in Dental Practice

For elderly patients, prescribed medications often require modifications in size and frequency of dose and duration of the prescription. Here, we discuss the prescription medications commonly used in daily dental practice — local anesthetics, analgesics and antibiotics — and modifications needed when prescribing for the elderly.

Local Anesthetics

In general, the use of local anesthesia in the dental office is considered safe when properly administered. No significant differences in the response of the elderly to local anesthetics are expected.³¹ However, as aging is accompanied by decreased liver and kidney function, doses well below the maximum are recommended.

Geriatric patients commonly have cardiovascular disease and, thus, the dose of epinephrine contained in anesthetics should be limited to a maximum of 0.04 mg. Even without a history of overt cardiovascular disease, it is prudent to minimize the use of epinephrine in elderly patients simply because of the expected effect of aging on the heart. Monitoring blood pressure and heart rate is advised when considering multiple administrations of epinephrine-containing local anesthetic.

Analgesics

The pharmacokinetic changes with aging, described above, lead one to expect that the geriatric patient will require a lower dose of analgesic medication.

Acetaminophen is the drug of choice for the control of mild to moderate pain in the elderly. At a recommended dose of 500–1000 mg every 4 h to a maximum of 4 g/day, this drug should be safe. However, acetaminophen has been implicated as one of the leading worldwide causes of drug overdose and acute liver failure. Ingestion of a single overdose or therapeutic misadventure may cause hepatotoxicity.³² Hepatic injury from acetaminophen is due mainly to a single toxic metabolite, N-acetyl-p-benzoquinone imine, which is formed by oxidation of the drug.^{33,34} Furthermore, in January 2014, the United States' Food and Drug Administration issued a statement advising that combination prescription pain relievers that contain more than 325 mg of acetaminophen per tablet, capsule or other dosage unit should no longer be prescribed because of the risk of liver toxicity.³⁵ Cases of severe hepatotoxicity have been reported in patients who took more than the prescribed dose of an acetaminophen-containing product in 24 h, took 2 or more acetaminophen-containing products simultaneously or combined alcohol with acetaminophen products.³⁵ Also, there is some evidence that oral anticoagulation therapy with warfarin may be potentiated by acetaminophen.³⁶ In these cases, decreasing the dose by half has been recommended.¹⁹

Chronic dosing, although uncommon in the dental setting, should be avoided in patients with decreased liver function or cirrhosis. In summary, in the elderly, acetaminophen has been proven to be broadly tolerable and have reasonable efficacy and a low side-effect profile. It is associated with few drug interactions, an important consideration in the elderly who are usually taking multiple medications. Thus, acetaminophen is considered safe for the elderly and without significant side effects when used appropriately.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have both anti-inflammatory and analgesic properties and, thus, their use in dentistry is advantageous. This group of drugs is widely used by the geriatric population, because of the high prevalence of chronically painful conditions, such as arthritis.³⁷ A number of NSAIDs have been shown to be effective for dental pain, including ibuprofen, naproxen, flurbiprofen, diflunisal and ketorolac. NSAIDs are highly lipid soluble and protein binding.³⁸ Their lipid solubility results in their widespread distribution in the elderly, who have increased stores of adipose tissue.³⁸ This, together with an increased concentration of the unbound drug and impaired renal function in the elderly, may lead to excessive drug levels and possible toxicity.

Furthermore, NSAIDs are associated with a number of adverse effects, the most important of which is their effect on the gastrointestinal tract. NSAIDs cause gastric erosion, which can lead to ulcers and then gastric bleeding. In the elderly, these effects tend to be more severe than in younger people. In fact, up to 16 000 patients die each year in the United States as a result of gastrointestinal complications from NSAID therapy.³⁹ Therefore, prescribing NSAIDs in a patient with active gastrointestinal disease is contraindicated, although it may be acceptable for a patient with a prior history of peptic ulcer.¹⁹

If it is necessary for a geriatric patient with gastrointestinal disease to take NSAIDs, there are 2 options. One is to prescribe ibuprofen with the prostaglandin analog, misoprostol. In a study by Silverstein and colleagues,⁴⁰ patients with rheumatoid arthritis receiving continuous NSAID therapy were randomly assigned to receive 800 µg of misoprostol or placebo a day. Serious gastrointestinal complications were reduced by 40% among patients receiving misoprostol compared with those receiving placebo. In patients with a history of peptic ulcer disease or gastrointestinal bleeding, misoprostol conferred a relative risk reduction of 52% and 50%, respectively.⁴¹ The second option, provided there are no significant risk factors for myocardial infarction or cerebrovascular accident, is to use the cyclo-oxygenase (COX)-2 inhibitor celecoxib, 200 mg twice a day, which is much less likely to cause gastric bleeding.

In summary, NSAIDs should be used with caution if there is a history of renal disease, significant cardiovascular disease or severe asthma.

In addition to severe adverse drug reactions, NSAIDs are associated with significant drug interactions. For instance, lithium clearance may be decreased by NSAIDs, resulting in increased serum concentration of lithium and toxicity.³³ It is not clearly understood who is predisposed to this interaction; however, elderly patients are likely susceptible.³³ Methotrexate may be displaced from its protein binding sites³³ by NSAIDs. This is generally not clinically relevant with low doses of methotrexate, as used for rheumatoid arthritis, but it is of serious concern when high doses are used for chemotherapy, in which case NSAIDs are contraindicated.³³ Because NSAIDs may also reduce renal blood flow, tubular excretion of drugs and renal prostaglandin production, they may attenuate the effects of the diuretic, beta-blocker and ACE inhibitor classes of anti-hypertensive drugs.^{42,43} NSAIDs also decrease the ability of the blood to clot and, therefore, increase bleeding; thus, people taking warfarin should avoid prolonged use of NSAIDs. In summary, in situations where acetaminophen would be insufficient to manage pain, it is acceptable to prescribe NSAIDs in the short term, i.e., < 5 days.

Opioid analgesics are effective in the treatment of moderate to severe pain in dentistry.⁴⁴ Although safe as a short-term analgesic, both the depth and duration of the effects of opioid analgesics are enhanced in the elderly.¹⁹ This is partly because of the pharmacokinetic and pharmacodynamic changes associated with aging, but there is also often a narrow therapeutic index for opioid analgesics related to hepatic and renal insufficiency and increased sensitivity to CNS drugs. For instance, meperidine is associated with an increased incidence of toxicity in the elderly.⁴⁵ Many adverse reactions to meperidine have been attributed primarily to the accumulation of its major metabolite, normeperidine.¹⁰ Thus, meperidine should be avoided.

Codeine, another analgesic commonly used in dentistry, is a weak opioid that has no analgesic effect on its own, but is converted to morphine by the liver enzyme CYP2D6. However, some people lack the ability to make this conversion because of low CYP2D6 enzyme levels. Moreover, the conversion can be inhibited by medications frequently prescribed for elderly patients, such as the SSRIs (e.g., fluoxetine, paroxetine and sertraline).⁴⁶ Also, codeine is often combined with other analgesic products (e.g., acetaminophen, ASA) resulting in analgesia greater than that produced by either agent alone. In the case of acetaminophen, it is important to ensure that the patient does not ingest more than 4 g a day of acetaminophen from all sources. In the case of ASA-containing formulations, care must be taken to ensure that there are no adverse renal or gastrointestinal effects. In patients taking COX-2 inhibitors, co-ingestion of ASA, even at low doses, can greatly increase the risk of upper-gastrointestinal bleeding.⁴⁷

Common side effects of opioid administration that are exacerbated in the geriatric patient may include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance and respiratory depression. In the older patient, the prevalence of constipation even without opiates is greater than 25%,⁴⁶ a tendency that puts them at increased risk of this side effect. In addition, immobility, dehydration and the use of other medications that slow bowel motility can magnify opioid-induced constipation.^{48,49}

Concurrent use of CNS depressant drugs can increase the risk of sedation and falls.^{33,50} Combinations of opioids and other CNS depressants, such as benzodiazepines, antidepressants and antipsychotics, may produce additive effects of sedation; for instance, the concurrent use of alcohol and opioid analgesics, which are both CNS depressants, may cause increased sedation.³³ As a general rule, because of the profound effect of opioids in the elderly and the increased likelihood of toxicity and adverse drug reactions, the dose and duration of use of opioid analgesics should be greatly limited. The degree of reduction of dose will be greater with increasing age, but a general guideline is to use half the recommended adult dose.¹⁹

As with all patients, optimal management of dental pain in the elderly is removal of its source. General recommendations for the use of analgesics in the geriatric patient are summarized in **Table 3**.

Table 3: General recommendations for the use of analgesics in elderly patients.

<p>General</p> <p>Eliminate the source of pain, if at all possible.</p> <p>Prescribed doses should be based on pain severity and medical history.</p> <p>Acetaminophen</p> <p>Acetaminophen is the analgesic of choice in the otherwise healthy elderly patient.</p> <p>Use a dose of 500–1000 mg every 4 h to a maximum of 4 g/day.</p> <p>Non-steroidal anti-inflammatory drugs (NSAIDs)</p> <p>NSAIDs are best avoided by elderly patients because of associated increased gastrointestinal problems.</p> <p>If NSAIDs are prescribed, use the lowest effective dose for the shortest possible time.</p> <p>Opioids</p> <p>Opioid analgesics are best avoided by elderly patients because they are associated with increased and more profound adverse drug reactions as well as prolonged durations of action.</p> <p>If opioid analgesics are prescribed, the dose should be lower than that for younger adults.</p>

Antibiotics

In general, no specific modifications in the pharmacotherapy of antibiotics are needed for the healthy geriatric patient.¹⁹ Beta-lactam antibiotics, which include the penicillins, are the most commonly used antibiotics in dental practice. Penicillins have not been shown to cause differential side effects or problems in older people compared with younger adults. Nonetheless, because renal excretion of penicillins and cephalosporins decreases with the physiological aging of the kidneys, dose reduction is advisable in elderly patients with renal disease.

Moreover, some unique features pertain to antibiotic administration in this population. For instance, pseudomembranous colitis is an important complication of antibiotic therapy in the elderly and is associated with high mortality.⁵¹ Because our geriatric patients often have multiple diseases, they are likely to be admitted to hospital, where they are likely to receive broad-spectrum antimicrobial drugs. Although all antibiotics have the potential to promote pseudomembranous colitis, certain drugs, such as clindamycin, broad-spectrum penicillins and second- and third-generation cephalosporins are most often implicated.^{50,51} Treatment includes discontinuation of the antibiotic and rehydration. These measures may suffice in approximately 20% of patients,

particularly those with mild disease. However, for patients not responding to these conservative measures within a few days, in cases where the offending antimicrobial agents cannot be discontinued or for patients with severe disease, specific therapy will be required.⁵² Oral vancomycin or metronidazole was found to be as effective.

In addition, geriatric patients are more susceptible to adverse drug reactions and drug interactions associated with antimicrobial therapy (Tables 4 and 5). For instance, the age-related physiological decline in kidney function, coupled with the severe renal effects associated with diabetes mellitus, congestive heart failure and hypertension, substantially influences the excretion of several antibiotics.⁵¹

Table 4: Antimicrobial-induced adverse drug reactions in elderly patients.

Antibiotic	Adverse drug reaction
Beta-lactam antibiotics	Diarrhea, drug fever, interstitial nephritis, thrombocytopenia, <i>Clostridium difficile</i> -associated colitis, rash, anemia, neutropenia
Clindamycin	Diarrhea and <i>Clostridium difficile</i> -associated colitis
Erythromycin, clarithromycin	Cholestatic hepatitis, <i>Clostridium difficile</i> -associated colitis
Azithromycin	QT prolongation, ototoxicity
Fluoroquinolones	Nausea, vomiting, QT prolongation
Tetracyclines	Photosensitivity
Doxycyclines	Esophageal ulcers

Sources: Becker (2014),³⁴ Kee (2012)⁵¹ and Faulkner et al. (2005).⁵³

Table 5: Antimicrobial-induced drug interactions in elderly patients.

Antibiotic	Interacting drug	Effect
Amoxicillin	Allopurinol	Rash
Fluoroquinolones	Pharmaceuticals containing aluminium, magnesium, iron or zinc	↓ absorption of fluoroquinolones
	Antiarrhythmic	Ventricular arrhythmia
Metronidazole	Warfarin	↑ effect of warfarin (monitor INR)
	Alcohol	Disulfiram-like reaction
	Phenytoin	↑ phenytoin levels
Azithromycin	Pharmaceuticals containing aluminium or magnesium	↓ absorption of azithromycin
Clarithromycin and erythromycin	HMG-CoA reductase inhibitors, cyclosporine, digoxin, warfarin, theophylline	↑ effect of interacting drug
Tetracyclines	Pharmaceuticals containing aluminium calcium, magnesium, iron and antacids	↓ absorption of tetracyclines
	Digoxin	↑ digoxin levels and risk of toxicity

Source: Faulkner et al. (2005).⁵³

Conclusion

Older people constitute a large and growing population. The typical older person has multiple diseases and is taking several medications; thus, administering drugs to elderly patients requires special care. Dentists must be aware that, as a group, the elderly are more susceptible to adverse drug reactions and drug interactions and, thus, must regularly review their patients' medical history

and medication list. Although pharmacotherapy is required at times, one must weigh the risks versus benefits before pharmacological intervention. As a general rule, if pharmacotherapy is initiated, it is important to follow the common advice: "start low, go slow." Finally, the dental practitioner is advised to work with the patient's physician, specialists and pharmacist to promote safe and effective pharmacotherapy.

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