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ABSTRACT

An adverse drug reaction (ADR) is an unwanted or harmful reaction following the administration of a drug or combination of drugs under normal conditions of use. An ADR is unpredictable and varies in severity, from minor side effects to severe complications such as organ damage, hospitalization, or even death. These unfortunate events are a significant concern in health care and lead to substantial increases in morbidity, mortality, and increased health-care costs. ADRs in dentistry are underreported and often overlooked, leading to a lack of awareness among dental professionals. In dentistry, ADRs can occur due to local anesthetics, antibiotics, antifungals, analgesics (opioid and nonopioid), anxiolytics, and muscle relaxants, all commonly used in the practice of dentistry. This course reviews some of the most prescribed medications in dentistry and their potential for ADRs. Further, it will underscore the need for improved pharmacovigilance in dental practice, including better reporting systems and education about ADRs for dental professionals. Finally, it emphasizes the importance of a thorough patient history, including medication history, to identify patients at risk of ADRs.

EDUCATIONAL OBJECTIVES

At the conclusion of this course, the oral health-care provider will be able to:

1. Identify the most commonly prescribed drugs in dentistry and their potential adverse reactions with a patient's existing drug regimen
2. Develop the ability to recognize the signs and symptoms of adverse drug reactions in dental patients
3. Review the necessary skills to assess patients' medical histories, including current medications, to avoid potential drug interactions
4. Review management of emergencies arising from adverse drug reactions, including understanding when and how to refer patients to appropriate medical facilities
5. Understand the importance of staying updated on new drugs, their uses in dentistry, and potential adverse reactions to ensure patient safety and effective treatment



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Avoiding adverse drug reactions in dentistry

A PEER-REVIEWED ARTICLE | by Eric Bornstein, DMD, BS

Fifty years ago, Karch and Lasagna reported in the *Journal of the American Medical Association* the following statements about ADRs:

“The data on adverse drug reactions (ADRs) are incomplete, unrepresentative, uncontrolled, and lacking in operational criteria for identifying ADRs. No quantitative conclusions can be drawn from the reported data in regard to morbidity, mortality, or the underlying causes of ADRs, and attempts to extrapolate the available data to the general population would be invalid and perhaps misleading.”¹

Almost half a century since the admonition from Karch and Lasagna, modern medicine still has

inadequately trained dentists and physicians to avoid ADRs. This is apparent from the recent ADR statistics reported by the Lown Institute:

“Every day, 750 older people living in the United States (age 65 and older) are hospitalized due to serious side effects from one or more medications. Over the last decade, older people sought medical treatment or visited the emergency room more than 35 million times for adverse drug events, and there were more than 2 million hospital admissions for serious adverse drug events. Older adults are hospitalized for adverse drug events at a greater rate than the

general population is hospitalized for opioids.”²

In dental medicine, we need to do better. ADRs pose significant risks to patients undertaking dental therapy, and our patient pool is aging rapidly.³

An ADR is defined as an unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use and is suspected to be related to the drug or a combination of drugs.⁴ Such a reaction is usually harmful and unintended and often requires discontinuation of the drug, dose reduction, or emergency intervention.^{5,6}

Table 1 gives a simple protocol for dealing with an adverse drug reaction.⁷

TABLE 1: Clinical responses to ADRs	
Immediate assessment	Assess the severity of the reaction. If it's severe, such as anaphylaxis, provide emergency treatment immediately. ⁸
Discontinuation of the drug	Stop the medication to prevent further harm. ⁹
Symptomatic treatment	If possible, administer medications to alleviate adverse symptoms—for example, antihistamines for allergic reactions or corticosteroids for inflammation. ¹⁰
Documentation and reporting	Document an ADR in the patient's dental record. Dentists are also encouraged to report an ADR to MedWatch, the FDA's monitoring program. ¹¹
Patient education	Inform the patient about the ADR, potential future risks, and alternative medications if necessary.
Follow-up	Follow-up appointments to monitor the patient's recovery are scheduled to ensure no further complications.

Local and systemic ADRs can occur when administering certain medications to a patient. These reactions can range from mild to severe and can affect multiple organ systems in the body.¹² For example, when a dental patient is prescribed antibiotics, local anesthesia with vasoconstrictors, opioids, or anxiolytics, they may experience a variety of systemic ADRs. Antibiotics, while crucial in combating bacterial infections, can lead to systemic ADRs, such as allergic reactions and gastrointestinal disturbances, or resistant pathogenic infections, such as *Clostridioides difficile* (*C. difficile*).^{13,14} Local anesthetics with

vasoconstrictors, used to prolong the effect of anesthesia and reduce bleeding, can cause systemic reactions such as hypertension, tachycardia, and, in rare cases, cardiovascular collapse. These reactions are particularly concerning in patients with preexisting heart conditions and on multiple cardiovascular and hemodynamic medications.^{15,16}

Opioids can cause severe respiratory depression, constipation, nausea, and dependence or addiction over time.¹⁷ Dental professionals must be aware of these potential systemic ADRs, monitor patients closely, and adjust treatment plans to ensure patient safety and effective treatment outcomes. Understanding the poten-

tial systemic ADRs associated with these medications is crucial in providing comprehensive patient care.

A dental professional must also differentiate between an ADR and an allergy. An allergy is an immune system response to a medication, such as anaphylaxis. In contrast, an ADR encompasses any unintended but noted effect of a drug, such as sedation. Such ADRs may be untoward or beneficial. While an allergy can be classified as an ADR, not all ADRs are allergies.¹⁸ A specific immunological response involving T-cells or drug-specific antibodies identifies a genuine drug allergy. These allergic

reactions can happen immediately or after a delay and can be potentially life-threatening.^{19,20}

Common symptoms of immediate drug allergies include urticaria, rhinitis, angioedema, bronchospasm, conjunctivitis, gastrointestinal (GI) upset, and anaphylaxis, the latter of which can cause cardiovascular collapse.²¹ Symptoms of delayed drug allergies typically manifest on the skin, including delayed urticaria, maculopapular eruptions, vasculitis, and blistering diseases.²²

Emergency medical services should be contacted in severe reactions, and the patient should be accompanied to the nearest emergency medical facility. The patient's physician should also be consulted to investigate the allergic reaction thoroughly.

In contemporary dental practice, only a few categories of pharmacological agents are widely used. These include local anesthetics (LA), central nervous system depressants (such as nitrous oxide, benzodiazepines, and general anesthetics), analgesics (such as nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids), and antibiotics (such as penicillin, azithromycin, doxycycline, clindamycin, and metronidazole). The dental health-care team must be well prepared to handle any foreseeable and unforeseeable ADRs in the dental office with any of these aforementioned medications.²³ Additionally, health-care professionals must thoroughly understand their patients' health statuses when prescribing new drugs or adjusting dosages to prevent avoidable ADRs.

Common ADRs seen in dental practice

Antibiotics: The prescription of antibiotics is a common practice for managing bacterial infections, especially those related to pulpal and periodontal conditions and peri- and

postoperatively during the delivery of surgical dental care.²⁴ Furthermore, antibiotics may be used prophylactically in some high-risk patients by reducing the risk of cardiac and joint complications due to bacteremia and addressing local complications following dental surgical procedures.²⁵ The use of antibiotics in dental infections is either empirical, relying on the anticipated microbial profile of odontogenic infections, or informed by antimicrobial susceptibility testing. Short courses of antibiotics, typically ranging from three to seven days, effectively manage most dental infections.²⁶

Amoxicillin, a beta-lactam antibiotic, remains the most commonly prescribed antibiotic in dental settings.²⁷ For patients with suspected or confirmed penicillin allergies, macrolide antibiotics such as azithromycin serve as an alternative treatment option.²⁸ Amoxicillin exhibits bactericidal properties by inhibiting peptidoglycan (cell wall) biosynthesis in the bacterial cells of susceptible organisms. Amoxicillin is the preferred initial treatment for most odontogenic infections.²⁹ The combination of amoxicillin and clavulanic acid, a beta-lactamase inhibitor, is also widely prescribed because it offers lower bacterial resistance and an extended spectrum of antimicrobial activity.³⁰ Amoxicillin is regarded as a relatively safe antibiotic, exhibiting the lowest reported incidence of ADRs among commonly used antibiotics.³¹ Amoxicillin, a widely used β -lactam antibiotic, can cause adverse reactions ranging from mild gastrointestinal symptoms and skin rashes to severe hypersensitivity reactions such as anaphylaxis, Stevens-Johnson syndrome, and drug-induced liver injury.

In contrast, metronidazole inhibits nucleic acid synthesis in susceptible bacteria through interactions

with intracellular macromolecules. Metronidazole is frequently prescribed as an adjunct to β -lactam antibiotics in the management of severe infections, such as severe and/or more aggressive forms of periodontitis (i.e., higher stage and/or grade periodontitis).³²

Additionally, metronidazole is effective in treating infections predominantly caused by anaerobic bacteria.³³ The mechanism of action of metronidazole in anaerobic bacteria involves several critical steps, culminating in the production of reactive nitro-radicals. These reactive intermediates interact with various cellular components of gram-negative pathogens, leading to extensive DNA damage. The bactericidal effect of metronidazole is concentration dependent, with higher concentrations resulting in more significant DNA damage and accelerated bacterial cell death.³⁴ Common medications that may interact with metronidazole include anticoagulants such as warfarin, astemizole, busulfan, cimetidine, disulfiram, and lithium.³⁵

It is also important to note that metronidazole should not be coadministered with alcohol due to the risk of a disulfiram-like reaction.³⁶ Metronidazole inhibits the enzyme acetaldehyde dehydrogenase within the ethanol degradation pathway, leading to an accumulation of acetaldehyde. This accumulation manifests clinically as flushing, headache, nausea, and cardiac palpitations. Consequently, patients are advised to avoid alcohol consumption during metronidazole therapy and for at least three days following the completion of metronidazole therapy.³⁷

Clindamycin, a lincosamide antibiotic, inhibits protein synthesis by reversibly binding to the 50S ribosomal subunits, making it a suitable alternative for patients sensitive to penicillin.³⁸ It is well regarded

for its excellent oral absorption, low incidence of bacterial resistance, and high antibiotic concentrations achieved in tissues, including bone. However, clindamycin is associated with a higher risk of *C. difficile* infections than other antibiotics commonly prescribed in dentistry.³⁹ Antibiotic-induced *C. difficile* infection occurs when broad-spectrum antibiotics disrupt the normal gut microbiota, allowing *C. difficile* to proliferate and produce toxins. The resulting imbalance in the gut flora leads to symptoms ranging from mild diarrhea to severe colitis, which can be life-threatening if not promptly treated.⁴⁰ If a patient exhibits watery diarrhea, abdominal pain with cramping or fever, and signs of dehydration, the antibiotic should be immediately discontinued, and a gastrointestinal consult should be requested.

Tetracyclines, a class of broad-spectrum antibiotics, have been widely used in dentistry for their effectiveness against various bacterial infections.²⁷ One of the primary advantages of tetracyclines is their ability to inhibit the growth of both gram-positive and gram-negative bacteria, making them versatile in treating periodontal diseases and other oral infections.⁴¹ Additionally, tetracyclines possess anti-inflammatory properties, which can be beneficial in managing conditions such as periodontitis. Their ability to concentrate in the gingival crevicular fluid further enhances their efficacy in treating periodontal infections.⁴² Moreover, tetracyclines inhibit collagenase activity, which helps preserve the connective tissue structure in periodontal disease.⁴³ Tetracyclines are also now recommended as a suitable antibiotic for subacute bacterial endocarditis (SBE) prophylaxis for penicillin-allergic patients instead of clindamycin.⁴⁴

The use of tetracyclines in

dentistry, however, is not without drawbacks. One of the most significant adverse effects is the potential for tooth discoloration, mainly when administered to children or pregnant women.⁴⁵ Tetracyclines can cause permanent discoloration of teeth when administered during tooth development, typically in children under the age of eight. The mechanism involves the deposition of tetracycline-calcium orthophosphate complexes in the dentin and enamel, leading to yellow, brown, or gray discoloration. Furthermore, the widespread use of tetracyclines has contributed to the development of antibiotic-resistant bacterial strains, which poses a significant challenge in clinical practice.⁴⁶ The risk of gastrointestinal disturbances, poor absorption when consumed with dairy products, and photosensitivity reactions are additional concerns associated with tetracycline use.⁴⁷ Therefore, while tetracyclines offer substantial benefits in dental treatments, their use must be carefully considered and balanced against these potential adverse effects.

Azithromycin, a widely used macrolide antibiotic in dentistry, can cause several ADRs ranging from mild to severe. Common mild ADRs include gastrointestinal disturbances such as nausea, vomiting, diarrhea, and abdominal pain. More severe reactions can involve hepatotoxicity, manifesting as elevated liver enzymes and, in rare cases, liver failure.⁴⁸ Azithromycin has also been associated with cardiovascular risks, including QT interval prolongation, which can lead to potentially fatal arrhythmias such as Torsades de pointes.⁴⁹ This can be especially problematic in patients who use cannabinoids.⁵⁰ Additionally, hypersensitivity reactions such as rash, pruritus, and, in rare instances, anaphylaxis may occur.⁵¹ Understanding

these ADRs is crucial for clinicians to balance the therapeutic benefits of azithromycin against its potential risks, ensuring patient safety and effective treatment outcomes.

Antifungals: Another primary risk associated with antibiotic use includes the development of opportunistic infections, notably oral candidiasis.⁵² Oral candidiasis, caused by *Candida albicans*, is typically managed through topical antifungal applications, such as miconazole or nystatin, or systemic treatments with fluconazole and itraconazole.⁵³ Topical antifungals such as nystatin are associated with mild adverse effects due to their limited systemic absorption. However, patient adherence to topical treatments, such as nystatin oral suspension, can be hindered by factors including its unpleasant taste, the need for frequent applications, and the extended duration of treatment.⁵⁴

While effective in treating fungal infections, systemic antifungal medications can cause a range of ADRs that vary depending on the specific drug and patient factors. Common ADRs include gastrointestinal disturbances such as nausea, vomiting, and diarrhea with oral antifungal agents such as fluconazole and itraconazole. Hepatotoxicity is another significant concern, particularly with azole antifungals, as these drugs can lead to elevated liver enzymes and, in severe cases, liver failure.⁵⁵

Beyond these common ADRs, antifungal medications can also cause more specific and severe reactions. The risk of drug interactions is also heightened with antifungals, as many of these agents are metabolized by the cytochrome P450 enzyme system, leading to potential interactions with other medications.⁵⁶

Before prescribing antifungal agents, a dentist must know the patient's current medications to prevent

potential adverse drug-drug interactions. This includes being vigilant about drugs metabolized by the cytochrome P450 enzyme system, such as certain statins, anticoagulants, and antiepileptics, as antifungal agents such as azoles can inhibit liver enzymes and lead to increased drug levels and toxicity.⁵⁷⁻⁵⁸ Additionally, dentists should consider the patient's use of immunosuppressants, as antifungals can interact with these medications, potentially leading to reduced efficacy or increased side effects.⁵⁹ By thoroughly reviewing the patient's medication history and understanding potential interactions, dentists can mitigate the risk of adverse reactions and ensure safe and effective antifungal therapy. Understanding these ADRs is crucial for clinicians to monitor and manage patients effectively, ensuring the benefits of antifungal treatment outweigh the risks.

Corticosteroids: In dental therapy, oral and topical corticosteroids serve various purposes. Oral corticosteroids are commonly used to alleviate pulpal and postoperative inflammation, while topical corticosteroids are effective in treating lichen planus.⁶⁰ However, the benefits of corticosteroids are accompanied by risks that depend on factors such as the route of administration (topical, oral, inhaled, intranasal, or intravenous), duration of treatment, type and strength of the corticosteroid, dosing schedule, and systemic conditions.⁶¹

Corticosteroids are categorized by dosage: low doses are 10 mg or less, moderate doses range from 15 to 40 mg, and high doses are over 40 mg. Potential side effects of short-term corticosteroid use include increased blood sugar levels and behavioral changes. There is also a need for steroid supplementation preoperatively in patients with a history of chronic corticosteroid use. In contrast, long-term use can result in osteoporosis,

oral candidiasis, cataracts, glaucoma, arthritis, hypertension, myopathy, and Cushing’s disease.^{62,63}

The concurrent use of corticosteroids and NSAIDs can lead to a range of ADRs due to their combined effects on the gastrointestinal tract and other systems by the inhibition of cyclooxygenase and the prevention of prostaglandin biosynthesis.⁶⁴ Both drug classes are known to cause GI irritation, and their simultaneous use significantly increases the risk of developing peptic ulcers and GI bleeding. Additionally, corticosteroids can cause fluid retention, high blood pressure, and impaired wound healing, while NSAIDs may lead to renal impairment and exacerbate hypertension.⁶⁵ The combination of these medications can also heighten the risk of cardiovascular events and contribute to the development of osteoporosis due to corticosteroid-induced calcium loss. Therefore, careful monitoring and consideration of alternative therapies are essential when potentially prescribing these drugs to mitigate likely adverse effects.⁶⁶

Also, the simultaneous use of corticosteroids and antihypertensive medications can lead to a range of adverse drug reactions due to their opposing effects on blood pressure regulation and fluid balance. Corticosteroids can cause fluid retention, leading to increased blood pressure and exacerbating hypertension.⁶⁷ This counteracts the intended impact of antihypertensive medications, which aim to lower blood pressure. Additionally, corticosteroids can induce electrolyte imbalances, which can further complicate the management of hypertension. The combination of these medications may also increase the risk of cardiovascular events, such as heart attacks and strokes.⁶⁸ Therefore, when prescribing these drugs together, careful monitoring and dose

adjustments are essential to mitigate potential adverse effects and ensure effective blood pressure control.

Table 2 lists ADRs that are possible when prescribing corticosteroids to patients already taking existing medications.^{69,70}

General anesthetic and sedative pharmacology: To ensure patient

sedation with diazepam may cause drowsiness, fatigue, and respiratory depression, which other central nervous system depressants can exacerbate.⁷⁴ Inhalation sedation with nitrous oxide, while generally safe, can result in nausea, vomiting, and dizziness—and its effects may be potentiated by other sedatives.⁷⁵ Intrave-

TABLE 2: Corticosteroid ADRs with other medications

Anticoagulants	Corticosteroids can affect blood clotting, which may require adjustments in anticoagulant dosages.
Anticonvulsants	These medications may have altered effectiveness when taken with corticosteroids.
Diabetes medications	Corticosteroids can raise blood sugar levels, potentially requiring adjustments in diabetes medication dosages.
HIV medications	Corticosteroids can interact with antiretroviral drugs, affecting their efficacy.
NSAIDs	The combination can increase the risk of gastrointestinal issues, such as ulcers and bleeding.
Vaccinations	Some vaccines may be less effective when administered to individuals taking corticosteroids.

comfort during extensive dental work, sedatives and general anesthetics are administered to induce sedation, modify consciousness, and ease anxiety.⁷¹ The dental profession typically categorizes these drugs into three groups: oral sedation (e.g., benzodiazepines), inhalation analgesia (e.g., nitrous oxide), and intravenous sedation (e.g., benzodiazepines, opioids, sedative-hypnotics). These classes of drugs commonly cause ADRs, such as nausea, vomiting, headaches, slurred speech, dry mouth, and dizziness.⁷² Respiratory depression is a significant ADR following the administration of sedatives and general anesthetics. The severity of adverse reactions typically depends on the sedation level and the number of agents administered, with more severe effects at higher doses and in combination therapy.⁷³

In dental patients with polypharmacy, the use of sedative medications can lead to a complex interplay of ADRs due to the combined effects of multiple medications. Oral

nous sedative medications can lead to hypotension, bradycardia, and respiratory depression, with an increased risk of these adverse effects in patients taking other cardiovascular or respiratory medications.⁷⁶ The combination of these sedation methods in a polypharmacy patient necessitates careful consideration of drug interactions, vigilant monitoring, and individualized dosing to ensure patient safety and minimize the risk of adverse reactions during dental procedures.

Nonnarcotic analgesics: The most common analgesics prescribed by dentists fall into two groups: nonnarcotic (acetaminophen and NSAIDs) and narcotic (opioids). Acetaminophen is preferred for mild dental pain when NSAIDs cannot be used. Acetaminophen is among the safest analgesics when administered to healthy individuals in typical therapeutic amounts.⁷⁷ However, there is a risk of hepatotoxicity due to the accumulation of N-acetyl-p-benzoquinone imine (NAPBQI), a potentially toxic

metabolite, in individuals with liver impairment (such as alcoholics) or in cases of overdose.⁷⁸ The commonly accepted maximum daily dose of acetaminophen for a healthy individual is 4,000 mg, although 3,000 mg is considered safer.⁷⁹

NSAIDs are widely prescribed for their analgesic, anti-inflammatory, and antipyretic properties, but their use is associated with a range of ADRs. One of the most significant concerns is their impact on the gastrointestinal tract.⁸⁰ NSAIDs inhibit the cyclooxygenase (COX) enzymes, which are crucial in producing prostaglandins and prostanoids that protect the stomach lining and intestines. This inhibition can lead to GI irritation, resulting in symptoms such as dyspepsia, nausea, and abdominal pain. More severe complications include the development of peptic ulcers, GI bleeding, and perforation, which can be life-threatening. The risk of these adverse effects is exceptionally high in elderly patients, those with a history of GI disorders, and individuals taking higher doses or prolonged courses of NSAIDs.⁸¹

In addition to GI complications, NSAIDs can also have adverse effects on the renal and cardiovascular systems.⁸² NSAIDs can cause renal impairment by reducing renal blood flow and glomerular filtration rate, leading to conditions such as acute kidney injury and chronic kidney disease. Patients with preexisting renal conditions, heart failure, or those taking other nephrotoxic medications are at increased risk.⁸³ Furthermore, NSAIDs can exacerbate hypertension and increase the risk of cardiovascular events, such as heart attacks and strokes, due to their effects on blood pressure regulation and platelet aggregation.⁸⁴ These risks necessitate careful patient selection, dose adjustments, and monitoring when prescribing NSAIDs, particularly in

individuals with underlying health conditions or those taking multiple medications.

Opioid analgesics: Opioids should be prescribed for dental pain only when nonopioid analgesics, such as NSAIDs and acetaminophen, are insufficient to manage moderate to severe pain. This typically occurs in cases of acute dental trauma, postsurgical pain, or severe infections. The decision to prescribe opioids should

be based on a thorough assessment of the patient’s pain level, medical history, and potential risk factors for opioid misuse. It is crucial to start with the lowest effective dose and to prescribe the smallest quantity necessary to manage the pain, typically for a duration of no more than three to seven days, to minimize the risk of dependency and adverse effects.

When titrating opioids for dental pain, it is essential to follow a

TABLE 3: FDA warnings for common opioids prescribed for dental pain

<p>From the FDA package insert for acetaminophen and codeine⁸⁷</p>	<p>Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of this drug, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications.</p> <p>Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.</p> <p>Patients receiving other narcotic analgesics, general anesthetics, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with acetaminophen and codeine may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.</p>
<p>From the FDA package insert for acetaminophen and hydrocodone⁸⁸</p>	<p>At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.</p> <p>In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.</p> <p>Hydrocodone may cause confusion and oversedation in the elderly. Elderly patients generally should be started on low doses of hydrocodone bitartrate and acetaminophen tablets and observed closely.</p>
<p>From the FDA package insert for aspirin and oxycodone⁸⁹</p>	<p>Oxycodone exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk prior to prescribing oxycodone and monitor all patients regularly for the development of these behaviors and conditions.</p> <p>Serious, life-threatening, or fatal respiratory depression may occur with use of oxycodone. Monitor for respiratory depression, especially during initiation of oxycodone or following a dose increase.</p> <p>Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.</p>
<p>From the FDA package insert for tramadol⁹⁰</p>	<p>Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous postmarketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range.</p> <p>Concomitant use of tramadol increases the seizure risk in patients taking selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics), tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or other opioids.</p> <p>Suicide risk: Do not prescribe tramadol for patients who are suicidal or addiction-prone.</p> <p>Prescribe tramadol tablets with caution for patients who are taking tranquilizers or antidepressant drugs and patients who use alcohol in excess and who suffer from emotional disturbance or depression.</p>

stepwise approach, starting with the least potent opioid and progressing to stronger medications only if necessary. Current recommendations from the ADA on the safe use of opioids for acute dental pain can be found in Carrasco-Labra et al.⁸⁵ As an example, Tramadol, a weak opioid agonist, can be initiated at a dose of 50–100 mg every four to six hours as needed, with a maximum daily dose of 300 mg. If pain persists and requires more potent analgesia, hydrocodone can be introduced at a dose of 5–10 mg every four to six hours, not exceeding 40 mg per day. For severe pain that is unresponsive to hydrocodone, oxycodone may be considered, starting at 5–10 mg every four to six hours, with a maximum daily dose of 30 mg. Throughout this process, careful monitoring for signs of opioid misuse, side effects, and overall pain management effectiveness is imperative to ensure patient safety and optimal outcomes. These patients should be carefully monitored because of the high risk of ADRs, including constipation.

Table 3 details the ADRs of commonly used dental opioid analgesics.⁸⁶

Local anesthetics and vasoconstrictors: Invasive dental procedures commonly use local anesthesia, including lidocaine, articaine, prilocaine, and mepivacaine.^{91,92} These anesthetics can be applied topically (though not all are available as topical preparations) or injected for local infiltration or nerve blocks. Local anesthetics are often combined with a vasoconstrictor such as epinephrine to prolong their duration of action and limit systemic absorption.⁹³

Although generally safe, local anesthetics can cause systemic and local toxicity due to the irritating nature of the solution, pressure from large volumes, or vasoconstriction. The dose and concentration should be customized for each patient to prevent

TABLE 4: Potential local anesthetic ADRs	
Allergic reactions	Although rare, some patients may experience allergic reactions to local anesthetics, particularly those in the ester group.
Toxicity	Overdose or inadvertent intravascular injection can lead to systemic toxicity, affecting the central nervous system and cardiovascular system.
Methemoglobinemia	Certain local anesthetics, such as prilocaine and benzocaine, can cause methemoglobinemia, a condition in which oxygen delivery to tissues is impaired.

TABLE 5: Potential vasoconstrictor ADRs	
Cardiovascular effects	Vasoconstrictors such as epinephrine can cause increased heart rate, elevated blood pressure, and palpitations. These effects are more pronounced in patients with cardiovascular disease.
Interaction with medications	Vasoconstrictors can interact with certain medications, such as beta-blockers, leading to exaggerated cardiovascular responses.
Local tissue effects	Prolonged vasoconstriction can reduce blood flow to the tissues, potentially leading to ischemia and tissue necrosis.

potential adverse reactions.

Tables 4 and 5 outline the adverse reactions associated with local anesthetics and vasoconstrictors.^{94,95}

Conclusion

This comprehensive analysis of ADRs in dental therapy underscores the critical and ongoing need for heightened awareness and careful patient assessment before any medication is prescribed or administered in the dental setting. The potential for allergic reactions, ranging from mild rashes to life-threatening anaphylaxis, remains a constant consideration. Furthermore, the risk of systemic toxicity affecting various organ systems and the possibility of adverse cardiovascular effects, such as arrhythmias or significant blood pressure changes, are important concerns. These risks are amplified in the increasing population of patients presenting with preexisting medical conditions and polypharmacy.

This course has highlighted the importance of a thorough and regularly updated medical and pharmacologic history. This is not merely a procedural step but a foundational element of safe dental practice. Understanding a patient’s current medications,

known allergies, past adverse reactions, and underlying health status—including hepatic and renal function—is crucial for anticipating and preventing potential ADRs. Equally important is the vigilant monitoring of patients both during and after dental procedures involving medications. This includes being vigilant for early signs of an adverse event and being prepared to manage it effectively.

Ultimately, this course should serve as a catalyst for proactively implementing robust pretreatment risk stratification protocols for adverse drug reactions within your daily practice and for committing to continuous learning and pharmacovigilance, staying updated on new drug interactions, and reporting any suspected ADRs to contribute to broader patient safety.

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QUESTIONS

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- What is the primary reason for monitoring ADRs in clinical dental practice?
 - To decrease the cost of health care
 - To ensure patient safety and improve therapeutic outcomes
 - To promote the use of generic medications
 - To reduce the workload of health-care professionals
- Which of the following is considered a serious adverse drug reaction?
 - Mild headache
 - Temporary rash
 - Anaphylactic shock
 - Nausea
- Which patient population is at higher risk for experiencing adverse drug reactions?
 - Young adults
 - Middle-aged men
 - Elderly and polypharmacy patients
 - Athletes
- What is the significance of reporting adverse drug reactions to MedWatch, the FDA's monitoring program?
 - To receive financial incentives
 - To contribute to the knowledge base for safer drug use
 - To avoid legal consequences
 - To promote brand-name drugs
- What is the most common type of adverse drug reaction associated with antibiotics?
 - Hepatotoxicity
 - Nephrotoxicity
 - Allergic reactions
 - Neurotoxicity
- Which antibiotic is most frequently associated with *C. difficile* infection?
 - Azithromycin
 - Amoxicillin
 - Clindamycin
 - Doxycycline
- Which of the following is a significant risk factor for developing antibiotic-associated diarrhea?
 - Age under 18
 - Short-term antibiotic use
 - Broad-spectrum antibiotic use
 - Use of topical antibiotics
- Which of the following is a common adverse drug reaction associated with antifungal medications?
 - Hypertension
 - Liver toxicity
 - Insomnia
 - Weight gain
- Which adverse drug reactions are commonly associated with antifungal use?
 - Gastrointestinal disturbances
 - Vomiting
 - Diarrhea
 - All of the above
- Which patient population is at higher risk for experiencing adverse drug reactions to antifungal medications?
 - Young adults
 - Patients with preexisting liver or kidney conditions
 - Athletes
 - Patients with no prior antifungal use
- Which of the following is a common adverse drug reaction(s) associated with long-term corticosteroid use?
 - Hypertension and osteoporosis
 - Fatigue
 - Insomnia
 - Weight loss
- Which patient population is at higher risk for experiencing adverse drug reactions to corticosteroids?
 - Young adults
 - Patients with preexisting diabetes or hypertension
 - Athletes
 - Patients with no prior corticosteroid use
- Which of the following is a common adverse drug reaction associated with NSAID use?
 - Hypertension and gastrointestinal bleeding
 - Tachycardia
 - Insomnia
 - Weight gain
- Which NSAID is most commonly prescribed for dental pain?
 - Ibuprofen
 - Celecoxib
 - Naproxen
 - Aspirin
- Why is it important to monitor patients for adverse drug reactions when prescribing NSAIDs?
 - To increase the duration of treatment
 - To prevent serious health complications and ensure effective treatment
 - To promote the use of over-the-counter NSAIDs
 - To reduce the cost of medication
- Which patient population is at higher risk for experiencing adverse drug reactions to NSAIDs?
 - Young patients
 - Patients with a history of GI, renal, or cardiovascular disease
 - Diabetics
 - Patients with no prior NSAID use
- Which of the following is a common adverse drug reaction associated with opioid use?
 - Hypertension
 - Constipation
 - Insomnia
 - Weight gain
- Which strong opioid medications are most commonly associated with causing serious respiratory depression?
 - Tramadol and codeine
 - Hydrocodone and oxycodone
 - Loperamide and buprenorphine
 - Tramadol and buprenorphine
- Why is it important to monitor patients for adverse drug reactions when prescribing opioids?
 - To increase the duration of opioid treatment
 - To prevent addiction and respiratory depression while ensuring effective pain management
 - To promote the use of generic opioids
 - To reduce the cost of opioid medication

20. Which patient population is at higher risk for experiencing adverse drug reactions to opioids?

- A. Patients under 18 years old
- B. Patients with a history of substance abuse or respiratory conditions
- C. Patients taking NSAIDs
- D. Patients with no prior opioid use

21. Which of the following is a common adverse drug reaction associated with local anesthesia containing vasoconstrictors?

- A. Hypertension
- B. Tachycardia
- C. Insomnia
- D. Weight gain

22. Which vasoconstrictor is most commonly used in local anesthesia to prolong its effect?

- A. Norepinephrine
- B. Epinephrine
- C. Dopamine
- D. Phenylephrine

23. Which patient population is at higher risk for experiencing adverse drug reactions to local anesthesia with vasoconstrictors?

- A. Patients with diabetes
- B. Patients with cardiovascular disease or hypertension
- C. Patients with neuropathy
- D. Patients utilizing statins for hypercholesterolemia

24. Which of the following is a common adverse drug reaction associated with anxiolytic use?

- A. Hypertension
- B. Sedation
- C. Insomnia
- D. Weight gain

25. Why is it important to monitor patients for adverse drug reactions when prescribing anxiolytics?

- A. To ensure the patient enjoys the experience
- B. To prevent serious health complications and ensure effective anxiety management
- C. To have the patient refer friends to the office
- D. None of the above

26. Which patient population is at higher risk for experiencing adverse drug reactions to anxiolytics?

- A. Patients taking NSAIDs
- B. Patients with a history of substance abuse or elderly patients
- C. Patients with autoimmune disease
- D. Patients with diabetic neuropathy

27. Which of the following is a common adverse drug reaction associated with conscious sedation?

- A. Hypertension
- B. Respiratory depression
- C. Tachycardia
- D. Hypoglycemia

28. Which conscious sedation medication is most commonly associated with causing hypotension?

- A. Midazolam
- B. Propofol
- C. Fentanyl
- D. Ketamine

29. Why is it important to monitor patients for adverse drug reactions when using conscious sedation?

- A. To ensure the patient enters REM sleep
- B. To prevent serious breathing complications and ensure patient safety
- C. To ensure proper analgesia
- D. None of the above

30. Which patient population is at higher risk for experiencing adverse drug reactions to conscious sedation?

- A. Patients with arthritis
- B. Patients with preexisting respiratory or cardiovascular conditions
- C. Patients with GI disease
- D. Patients with allergies

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Avoiding adverse drug reactions in dentistry

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EDUCATIONAL OBJECTIVES

1. Identify the most commonly prescribed drugs in dentistry and their potential adverse reactions with a patient's existing drug regimen
2. Develop the ability to recognize the signs and symptoms of adverse drug reactions in dental patients
3. Review the necessary skills to assess patients' medical histories, including current medications, to avoid potential drug interactions
4. Review management of emergencies arising from adverse drug reactions, including understanding when and how to refer patients to appropriate medical facilities
5. Understand the importance of staying updated on new drugs, their uses in dentistry, and potential adverse reactions to ensure patient safety and effective treatment

COURSE EVALUATION

1. Were the individual course objectives met?
Objective #1: Yes No Objective #3: Yes No Objective #5: Yes No
Objective #2: Yes No Objective #4: Yes No

Please evaluate this course by responding to the following statements, using a scale of Excellent = 5 to Poor = 0.

- | | | | | | | |
|--|---|---|---|---|-----|----|
| 2. To what extent were the course objectives accomplished overall? | 5 | 4 | 3 | 2 | 1 | 0 |
| 3. Please rate your personal mastery of the course objectives. | 5 | 4 | 3 | 2 | 1 | 0 |
| 4. How would you rate the objectives and educational methods? | 5 | 4 | 3 | 2 | 1 | 0 |
| 5. How do you rate the author's grasp of the topic? | 5 | 4 | 3 | 2 | 1 | 0 |
| 6. Please rate the author's effectiveness. | 5 | 4 | 3 | 2 | 1 | 0 |
| 7. Was the overall administration of the course effective? | 5 | 4 | 3 | 2 | 1 | 0 |
| 8. Please rate the usefulness and clinical applicability of this course. | 5 | 4 | 3 | 2 | 1 | 0 |
| 9. Please rate the usefulness of the references. | 5 | 4 | 3 | 2 | 1 | 0 |
| 10. Do you feel that the references were adequate? | | | | | Yes | No |
| 11. Would you take a similar course on a different topic? | | | | | Yes | No |

12. If any of the continuing education questions were unclear or ambiguous, please list them.

13. Was there any subject matter you found confusing? Please describe.

14. How long did it take you to complete this course?

15. What additional dental continuing education topics would you like to see?

Mail/fax completed answer sheet to:

Endeavor Business Media

Attn: Dental Division; 7666 E. 61st St. Suite 230, Tulsa, OK 74133
Fax: (918) 831-9804

Payment of \$69 is enclosed (this course can be completed online for \$39. Scan the QR code or go to dentalacademyofce.com to take advantage of the lower rate).

Make check payable to Endeavor Business Media

If paying by credit card, please complete the following:

MC Visa AmEx Discover

Acct. number: _____

Exp. date: _____ CVC #: _____

Billing address: _____

Charges on your statement will show up as Endeavor.

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|---------------------|---------------------|
| 1. (A) (B) (C) (D) | 16. (A) (B) (C) (D) |
| 2. (A) (B) (C) (D) | 17. (A) (B) (C) (D) |
| 3. (A) (B) (C) (D) | 18. (A) (B) (C) (D) |
| 4. (A) (B) (C) (D) | 19. (A) (B) (C) (D) |
| 5. (A) (B) (C) (D) | 20. (A) (B) (C) (D) |
| 6. (A) (B) (C) (D) | 21. (A) (B) (C) (D) |
| 7. (A) (B) (C) (D) | 22. (A) (B) (C) (D) |
| 8. (A) (B) (C) (D) | 23. (A) (B) (C) (D) |
| 9. (A) (B) (C) (D) | 24. (A) (B) (C) (D) |
| 10. (A) (B) (C) (D) | 25. (A) (B) (C) (D) |
| 11. (A) (B) (C) (D) | 26. (A) (B) (C) (D) |
| 12. (A) (B) (C) (D) | 27. (A) (B) (C) (D) |
| 13. (A) (B) (C) (D) | 28. (A) (B) (C) (D) |
| 14. (A) (B) (C) (D) | 29. (A) (B) (C) (D) |
| 15. (A) (B) (C) (D) | 30. (A) (B) (C) (D) |

CUSTOMER SERVICE: (800) 633-1681

EXAM INSTRUCTIONS. All questions have only one answer. If mailed or faxed, grading of this examination is done manually. Participants will receive confirmation of passing by receipt of a Verification of Participation form. The form will be mailed within two weeks after receipt of an examination.

COURSE EVALUATION AND FEEDBACK. We encourage participant feedback. Complete the evaluation above and e-mail additional feedback to Rachel McIntyre (rmcintyre@endeavorb2b.com) and Laura Winfield-Roy (lwinfield@endeavorb2b.com).

COURSE CREDITS AND COST. All participants scoring 70% or higher on the examination will receive a verification form for three (3) continuing education (CE) credits. Participants are urged to contact their state dental boards for CE requirements. The cost for courses ranges from \$20 to \$110.

CANCELLATION AND REFUND POLICY. Participants who are not 100% satisfied can request a refund by contacting Endeavor Business Media in writing.

RECORD KEEPING. Endeavor Business Media maintains records of your successful completion of any exam for a minimum of six years. Please contact our offices for a copy of your CE credits report. This report, which will list all credits earned to date, will be generated and mailed to you within five business days of receipt.

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