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Adverse drug interactions in dentistry

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According to the United States Food and Drug Administration web site, there are more than 15,000 currently approved prescription and over-the-counter drugs, diagnostics and intravenous supplementation products in the United States (78). Couple these with the hundreds of herbal and dietary supplements that undergo little if any scrutiny by the Food and Drug Administration (48), and it is no wonder that the potential for adverse drug interactions is a growing concern for all fields of patient care including dental medicine. To further complicate matters, common food products, such as grapefruit juice, that are consumed by many patients because of their reported cardiovascular and cancer-preventing benefits, have been involved in some of the most serious adverse drug interactions reported to date (19, 74, 158).

There is no doubt that our patient population is consuming more and more drugs and herbal products. The geriatric dental population is increasing (75) and because of the presence of multiple disease states such as hypertension, congestive heart failure, diabetes, arthritis, and osteoporosis in these individuals, polypharmacy in this population is the norm (99, 182). In addition, decreases in cardiac output resulting in less blood flow and less drug being presented to the liver and kidney, decreases in hepatic and pre-hepatic drug metabolizing efficiency, decreases in renal excretory ability and increased receptor sensitivity to a variety of the central nervous system-acting drugs such as antidepressants, narcotics, and benzodiazepines, and a progressive decline in counter-regulatory (homeostatic) mechanisms make this population especially vulnerable to the adverse effects of drugs (232). Unlike 30 years ago, when many of these patients were coming to dental practices completely or partially edentulous, these patients are now maintaining their teeth longer and even when there is risk of tooth loss or there are edentulous spaces, many of these patients are opting for complex periodontal, implant, and restorative procedures over full or partial dentures (60). As a consequence, these patients need local anesthesia / vasoconstrictors, analgesics, anxiolytics, and antibiotics, which on occasion could adversely interact with a variety of the medications they are on.

Even among young to middle-aged adults, the intake of certain prescription medications, especially those within the cardiovascular classes of drugs, is on the rise. With the new guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, patients with what was previously considered 'normal' or 'borderline' blood pressure are now being placed on a variety of antihypertensive agents (45). Patients with concomitant cardiovascular risk factors such as diabetes are being more aggressively treated, with multi-drug regimens often being recommended at the initiation of antihypertensive therapy.

Classes of drugs that did not exist 20 years ago are being widely administered to young and old alike. On December 29, 1987, fluoxetine (Prozac®) became the first selective serotonin reuptake inhibitor approved by the Food and Drug Administration for the treatment of adult depression (233). Today there are five selective serotonin reuptake inhibitors in the top 100 prescribed drugs in the United States (229). In addition to adult depression, they are being prescribed for a variety of psychiatric conditions including childhood depression, social anxiety disorder, general anxiety disorder, panic attacks, and obsessive–compulsive disorder. Because of their more recent arrival on the market compared to other drug classes, our knowledge of potential adverse drug interactions with these agents is still evolving.

Like the geriatric patient population, the pediatric dental patients have their own unique physiology and anatomy compared to young adult patients that

appear to make the young child especially vulnerable to drug interactions involving multiple central nervous system depressant drugs (244). In particular, the outcomes of combining supratherapeutic dosages of local anesthetics with narcotic sedatives have been devastating in this patient population (93, 167). Besides frank overdoses of one or both components, narrow nares, a large tongue, a high glottis, slanting vocal cords, a generally smaller diameter of the airway passages, a high basal metabolic rate, and possibly even increased receptor sensitivity all appear to contribute to some of the tragic outcomes in these situations (244).

Our goal in this manuscript is to try to make 'some sense' of the myriad of potential adverse drug interactions that are reported in the literature with a particular emphasis on those that are clinically relevant to the periodontist and general dentist. Instead of just using a 'cook-book approach', an understanding of the general mechanisms behind most adverse drug interactions will aid the clinician in identifying potential drug interactions before they occur.

General mechanisms of adverse drug interactions

Therapeutic index of an interacting drug

A review of a major drug interaction text finds seven pharmacologically unrelated agents with respect to mechanisms of action and therapeutic category to be among the most frequent 'culprits' involved in clinically significant adverse drug interactions with a multitude of other drugs (221). They are, in alphabetical order, cyclosporine – an immunosuppressant widely used to prevent organ transplant rejection, digoxin – a sodium/potassium ATPase pump inhibitor which was among the first drugs to show effectiveness in the treatment of congestive heart failure, lithium carbonate – with diverse actions in the central nervous system and still a mainstay in the treatment of bipolar disorder, methotrexate – a folic acid synthesis inhibitor used in the treatment of various cancers and more recently in slowing the joint destruction of rheumatoid arthritis, phenytoin – a sodium channel blocker in the central nervous system with potent anticonvulsant activity, theophylline – a phosphodiesterase inhibitor and adenosine receptor antagonist employed frequently in severe asthma, and warfarin – an inhibitor of vitamin K-dependent clotting factors and the prototype antithrombotic agent. While two of these drugs, phenytoin and warfarin possess additional properties that make them even more poised for clinically significant drug interactions (the enzyme-inducing properties of phenytoin and the high protein-binding of warfarin and phenytoin), all seven share the common property of possessing a low therapeutic index; that is the difference between their effective dose and a potentially lethal dose of the drug is relatively small. By definition the therapeutic index is defined as the ratio of the median lethal dose (LD_{50}) to the median effective dose (ED_{50}). Therapeutic indices of the seven drugs described range between two and five, meaning that relatively small increases in their blood levels, sometimes as the result of a diminution in their metabolism or excretion by other drugs, can lead to potentially lethal side effects. It is one of the reasons why blood levels of drugs like lithium, digoxin, phenytoin and theophylline are routinely monitored and why a surrogate measure reflecting the ability of blood to coagulate, such as the international normalized ratio, is routinely performed in patients taking warfarin therapy (59, 197). For example, accepted therapeutic blood levels of theophylline are in the 10–20 mg/l range (23). A theophylline blood level of 30 mg/l, representing only a 50% increase above the top end of the therapeutic range, is often associated with tremors, tachycardia, cardiac arrhythmias, and seizures (18, 212). In addition, because these drugs possess a narrow therapeutic window and are typically employed for potentially life-threatening conditions (e.g. digoxin for congestive heart failure, warfarin to prevent stroke or myocardial infarction) or debilitating conditions (lithium to prevent manic depressive episodes), drugs that induce relatively small decreases in their blood levels can readily cause them to fall below their therapeutic range, leading to potentially disastrous effects as the result of the exacerbation of the very disease that they are being used to treat.

Pharmacokinetic mechanisms of drug interactions

Pharmacokinetic drug interactions involve the ability of one drug to alter the absorption, distribution, biotransformation (metabolism) or excretion of another drug (221). Of this group, alterations in biotransformation tend to occur most frequently and account for some of the most potentially serious drug interactions that are discussed in this paper.

Drug absorption interactions

These types of pharmacokinetic interactions typically involve two drugs or a drug and a food product that are administered by mouth. The drug or food product then impairs the ability of the other drug to cross mucous membranes in the stomach and small intestine, a process necessary for the drug to enter the bloodstream, ultimately reducing its blood levels and effectiveness. A central dogma in clinical pharmacology is that unless a drug enters the bloodstream it really has not entered the body *per se* because the blood acts as the conduit to the drug's site of action or receptors. For example, the antifungal agent ketoconazole is more completely absorbed at highly acidic pHs, so antacids, histamine-2 receptor blockers (i.e. cimetidine and ranitidine), and proton pump inhibitors (i.e. omeprazole and esomeprazole) can significantly reduce the absorption and anti-fungal efficacy of this drug (43, 193, 235). Drug absorption interactions more familiar to dental practitioners include the ability of systemic tetracycline and quinolone (i.e. ciprofloxacin) antibiotics to chelate drugs (i.e. antacids, vitamins, and iron supplements) and foods (dairy products) that contain divalent and trivalent cations (i.e. Al^{3+}, Bi^{2+}, Ca^{2+}, Fe^{2+}, Mg^{2+}, and Zn^{2+}) resulting in the formation of poorly absorbed antibiotic–cation complexes and sub-therapeutic blood concentrations of the antibiotic (143, 181). Figure 1 illustrates the results of an interaction with tetracycline and milk.

Drug displacement (protein-binding) interactions

Following their absorption into the bloodstream, most drugs exhibit varying degrees of plasma protein binding; that is they reversibly bind to albumin and other plasma proteins via ionic interactions. Only drug that is unbound in the plasma is free to interact with its receptors. Since there is a finite number of protein-binding sites, clinically significant interactions can occur when two highly protein-bound drugs (typically >90%) are given concomitantly and compete for these sites. The usual scenario is that one of the highly protein-bound drugs possesses a relatively low therapeutic index and is displaced from plasma protein-binding sites by a so called highly protein-bound displacer drug (46). Potential displacer drugs employed in dentistry include the non-steroidal anti-inflammatory drugs, salicylates, diazepam, and chloral hydrate. The drug that is displaced is now free in the plasma at supratherapeutic blood levels, potentially resulting in a clinical scenario resembling an overdose of the displaced drug.

Take for example the potential adverse drug interactions reported between warfarin and the non-steroidal anti-inflammatory drugs ibuprofen or naproxen. Warfarin, a drug with a low therapeutic index, is approximately 99% protein-bound, which means at any given time (assuming that warfarin is being administered in its therapeutic range) only 1% of warfarin is free in the bloodstream to interact with its receptors. A short analgesic course of ibuprofen or naproxen, which themselves are reported to be 99% protein-bound (46), could theoretically reduce warfarin's protein binding to only 97%, which now equates to 3% of the drug being free in the plasma. While at first glance this appears to be a minor change in warfarin's equilibrium, it really represents a three-fold increase in free blood levels of warfarin, greatly increasing the chance of a bleeding episode. Potential drugs with high protein binding and low therapeutic indices that appear to be delicately poised for adverse drug interactions with displacer drugs are shown in Table 1.

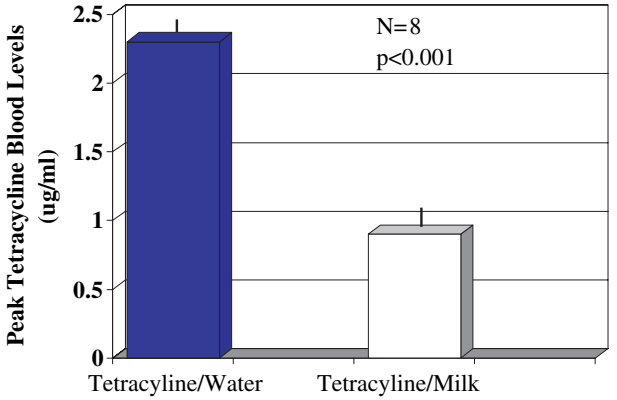

Fig. 1. Mean peak blood levels (±SEM) of a single dose of oral tetracycline hydrochloride 250 mg when administered with water or milk. Data adapted from Leyden JJ. *Am Acad Dermatol* 1985: 12: 308–312.

Table 1. Plasma protein binding characteristics of various drugs and the potential result of their displacement

Drug	% Protein-bound	Displacement result
Warfarin	99	Bleeding
Tolbutamide, chlorpropamide, glyburide, other sulfonylureas	90–99	Hypoglycemia
Phenytoin	90	Central nervous system depression, ataxia

Most pharmacokinetic experts now agree that these types of protein-binding–drug displacement interactions may not be as clinically significant as once thought because of homeostatic compensatory mechanisms, and other types of interactions which are simultaneously occurring may more fully account for the deleterious sequelae reported (209). In the case of warfarin and non-steroidal anti-inflammatory drugs, an additive pharmacodynamic interaction where two drugs with distinct pharmacological mechanisms on clotting profile (an inhibition of vitamin K-dependent clotting factors for warfarin and an inhibition of cyclooxygenase-1 resulting in anti-platelet activity and a diminution of cytoprotection for non-steroidal anti-inflammatory drugs) are thought to be more important factors in the increased gastrointestinal bleeding risk posed by the combination (214).

Drug biotransformation (metabolic) interactions

Although some drugs like penicillin are largely excreted unchanged, most drugs undergo some degree of biotransformation before elimination. Often used interchangeably, biotransformation is the preferred term over metabolism because metabolism implies that the drug is made less active or inactive. While this process via enzymatic catalysis typically either inactivates the drug or at the very least makes the drug less lipid soluble, more polar and more readily excreted, active metabolites as in the case of diazepam are often formed (164), and in a few cases the parent compound is an inactive prodrug requiring enzymatic transformation in the small intestine and liver for therapeutic activity as in the cases of codeine and tramadol (68, 138). While the liver is the principal organ involved in these processes, most tissues in the body, including the small intestine, kidney, neuronal tissue, and bloodstream, can participate depending on the drug or endogenous compound. For drugs administered orally that possess a high first-pass effect (i.e. a large percentage of the drug is chemically altered before entering the blood-stream), pre-hepatic biotransformation in the small intestine is now known to be an important site for metabolic drug interactions (166).

With respect to drug interactions affecting metabolic enzymes, two basic processes can occur. Enzymes that metabolize a group of drug substrates can be induced by other drugs; this means that the production of these enzymes is up-regulated typically resulting in a diminished effect of the substrate drug. Well-known enzyme inducers that reduce the blood levels of a variety of drugs include members of the barbituric acid class such as phenobarbital and the antituberculosis antibiotic rifampin (102, 159). For example, the ability of rifampin ingestion to reduce both the blood levels and the efficacy of oral contraceptives has been well documented (6, 65).

At the other end of the spectrum, certain drugs and chemicals can competitively compete with a drug substrate's enzyme-binding sites, producing the phenomena of enzyme inhibition (159). The end result of this type of interaction is a diminished biotransformation of the substrate drug leading to an exaggerated pharmacological effect resembling an overdose of the substrate drug, unless the substrate drug is a prodrug. For example, the ability of erythromycin (an enzyme inhibitor) to reduce the metabolism of theophylline (a drug substrate) can lead to dysrhythmias, tremors, and seizures (189). In the presence of enzyme inhibitors, the toxicities resulting from these types of interactions have contributed to the removal of several widely marketed substrate drugs from the U.S. marketplace, including the cholesterol-lowering drug cerivastatin because of an unusually high incidence of rhabdomyolysis, and both the non-sedating antihistamines astemizole and terfenadine and the gastroesophageal reflux drug cisapride for a number of reports of life-threatening ventricular arrhythmias known as torsades de pointes (Table 2) (118).

It has been well recognized for at least the last 15 years that the biochemical target for the vast majority of these drug metabolic interactions is the cytochrome P450 system (106). The cytochrome P450 system is a group of heme-containing enzymes embedded primarily in the lipid bilayer of the smooth endoplasmic reticulum of hepatocytes in the liver and enterocytes in the small intestine. These enzymes are involved in the oxidative metabolism of a number of drug classes, as well as a variety of endogenous substances, such as steroid hormones. The current nomenclature of these enzymes employs a three-tier system; CYP followed by a number representing the family of enzymes, a letter representing the subfamily, and then another number representing the individual gene (i.e. CYP3A4) (55, 159). Each individual enzyme is termed an isoform or isoenzyme. There have been more than 30 cytochrome P450 isoenzymes identified to date, with the major ones responsible for drug metabolism being CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A4. The human CYP3A4 isoform is the most abundant cytochrome family expressed in the human liver and intestine, and is thus involved in the metabolism of a greater number of drugs and a greater proportion of adverse

Table 2. Abbreviated table of CYP-450 enzyme substrates, inducers and inhibitors

CYP isoform	Substrates	Inducers	Inhibitors
CYP1A2	**Anti-Alzheimer**: tacrine **Antiasthmatic**: theophylline **Antidepressants**: fluvoxamine, imipramine **Antipsychotics**: clozapine, halperidol	**Antibiotic**: rifampin **Anticonvulsant**: carbamazepine **Foods**: char-grilled meats **Recreational drug**: tobacco	**Antibiotics**: ciprofloxacin, erythromycin, ofloxacin **Antidepressant**: fluvoxamine
CYP2C9	**Angiotensin-2 receptor blockers**: ibresartan, losartan **Anticoagulant**: warfarin **Anticonvulsant**: phenytoin **Hypoglycemics**: glipizide, glyburide, tolbutamide **Non-steroidal anti-inflammatory drugs**: diclofenac, ibuprofen, naproxen	**Antibiotic**: rifampin **Barbiturates**: phenobarbital, secobarbital	**Antibiotic**: metronidazole **Antidepressants**: fluvoxamine, paroxitene, sertraline **Antifungal**: fluconazole
CYP2D6	**Antidepressants**: amitriptyline, desipramine, imipramine, paroxitene **Antipsychotics**: halperidol, risperidone **Beta-blockers**: metoprolol, propranolol, timolol **Narcotic analgesics**: codeine, hydrocodone, tramadol	**Antibiotic**: rifampin **Corticosteroid**: dexamethasone	**Antidepressants**: fluoxetine, paroxitene, sertraline **Antiarrhythmic**: amiodarone **H1 receptor blockers**: hydroxyzine, promethazine
CYP2E1	**Alcohol**: ethanol **General anesthetics**: enflurane, halothane, isoflurane, sevoflurane **Muscle relaxer**: chlorzoxazone **Non-narcotic analgesic**: acetaminophen	**Antibiotic**: isoniazid **Recreational drugs**: ethanol, tobacco	**Alcoholism rehabilitation agent**: disulfiram
CYP3A4	**Antibiotics**: clarithromycin, erythromycin **Anticoagulant**: warfarin **Anticonvulsant**: carbamazepine **Antipsychotics**: haloperidol, pimozide **Benzodiazepines**: alprazolam, diazepam, midazolam, triazolam **Calcium channel blockers**: amlodipine, diltiazem, felodipine, verapamil **Cholesterol-lowering drugs**: atorvastatin, cerivastatin*, lovastatin, simvastatin **Corticosteroids**: hydrocortisone, methylprednisolone **H1 receptor blockers**: astemizole*, terfenadine* **HIV protease inhibitor**: idinavir, nelfinavir, ritonavir, saquinavir **Hormonal agents**: estrogens, progestins **Immunosuppressants**: cyclosporine, tacrolimus **Local anesthetic**: lidocaine **Prokinetic agent**: cisapride*	**Antibiotic**: rifampin **Anticonvulsants**: carbamazepine, phenytoin **Barbiturates**: phenobarbital, secobarbital **Corticosteroids**: dexamethasone, hydrocortisone, prednisolone, methylprednisolone **Herbal remedy**: St John's wort **HIV reverse transcriptase inhibitors**: efavirenz, nevirapine **Hypoglycemics**: pioglitazone, troglitizone	**Antibiotics**: clarithromycin, erythromycin **Antidepressants**: fluvoxamine, nefazodone **Antifungals**: clotrimazole, fluconazole, itraconazole, ketoconazole **Calcium channel blockers**: diltiazem, verapamil **Foods**: Grapefruit juice, Seville oranges **H2 receptor blocker**: cimetidine **HIV protease inhibitors**: idinavir, nelfinivir, ritonavir, saquinavir

HIV, human immunodeficiency virus; H1, histamine H1; H2, histamine H2.
*Removed from U.S. marketplace.

drug:drug interactions (241). As shown in Table 2 drugs can be substrates, inducers or inhibitors of the various cytochrome P450 isoenzymes. A more complete and constantly updated list of these drugs with appropriate links can be found on the World Wide Web (82).

Note that with respect to drugs often employed in dentistry, several benzodiazepines and narcotic analgesics appear in the substrate listings, while several commonly employed antimicrobial agents appear as enzyme inhibitors. While these types of interactions become most significant with chronic administration of a cytochrome P450 substrate and a corresponding cytochrome P450-inducing or -inhibiting drug, short-term administration especially with respect to enzyme-inhibiting drug interactions, can produce clinically significant increases in substrate blood levels resulting in potentially toxic pharmacological effects. For example, peak blood levels of a single 6 mg oral dose of midazolam are approximately doubled following the intake of ten ounces (280 g) of grapefruit juice two hours before midazolam dosing (96). While midazolam possesses a relatively high therapeutic index, over-sedation with an increased risk of obstruction is a possible outcome of this interaction if it were to occur in a pediatric dental patient undergoing a sedation procedure.

Drug excretion interactions

Since the kidney is the primary organ of drug elimination, the ability of one drug to impair the renal elimination of another drug can result in supratherapeutic blood levels of the drug being retained. As with other types of interactions resulting in systemic drug accumulation, a retained drug with a low therapeutic index is of most clinical concern. Compare for example the ability of probenecid to inhibit the active renal secretion of penicillin, a drug with an extremely high therapeutic index. Not only is there virtually no toxicity with this interaction but it has been clinically employed in the past when supplies of the antibiotic were scarce to prolong penicillin's action. On the other hand, the ability of non-steroidal anti-inflammatory drugs, including ibuprofen, diclofenac, and naproxen, to inhibit the renal excretion of lithium, a drug with a very low therapeutic index, can lead to severe central nervous system and renal toxicity (198).

Over the last 10 years evidence has been mounting that a number of adverse drug interactions at least partially involve the ability of certain agents to modulate the energy-dependent multi-drug efflux pump known as P-glycoprotein (101). P-glycoprotein is expressed on numerous tissues including the brush-border membranes of the luminal epithelium of the small intestine and the canilicular surface of hepatocytes, pumping a number of drugs back into the intestinal lumen and decreasing drug bioavailability (129). As with the cytochrome P450 system, drugs can be substrates, inducers or inhibitors of P-glycoprotein; an inducer decreasing and an inhibitor increasing substrate bioavailability. Intriguingly, there is considerable overlap between CYP3A4 and P-glycoprotein substrates, inducers, and inhibitors. For example, the herbal antidepressant agent St John's Wort, is an inducer of both systems possibly explaining its ability to reduce blood levels of certain drugs beyond that predicted by CYP3A4 induction alone (101). On the other hand, digoxin bioavailability appears to be more exclusively influenced by P-glycoprotein activity than by CYP3A4, and recent reports of increased plasma levels of this drug reported with concomitant clarithromycin administration, appear to involve the latter drug's ability to inhibit P-glycoprotein activity (202). While beyond the scope of the current paper, the existence of a P-glycoprotein efflux pump on the luminal surface of brain capillary endothelial cells may be of significant clinical relevance concerning drug interactions involving drug entry into the central nervous system (128).

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions occur at the site of drug action, more specifically at the receptor level. At one end of the spectrum these interactions can be additive, where the end result is a simple summation of the two drug effects, or they can be potentiating, where the ultimate pharmacological effect is greater than the simple sum of either drug action alone (255). However, these terms are often used rather loosely because in man it is often difficult to distinguish if the ultimate effect was simply additive or supra-additive. These additive or supra-additive interactions can occur between two drugs that occupy the same class of receptors, as in the case of administering the anticholinergic drug atropine to dry the mouth in a patient who is already taking the tricyclic antidepressant drug amitriptyline, which also possesses potent anticholinergic activity. This combination can lead to excessive antagonism of muscarinic cholinergic receptors in both the periphery and the central nervous system resulting in blurred vision, inability to sweat with possible hyperthermia, urinary retention, constipation, tachycardia, confusion, and hallucinations. These adverse interactions can also occur between two drugs that occupy distinct receptors. The additive effects of combining narcotic analgesics with alcohol, two central nervous system depressants that occupy distinct receptors in the brain, are certainly well known among clinicians who

prescribe analgesic agents. More recently, reports of what appears to be a supra-additive interaction at distinct receptors between non-steroidal anti-inflammatory drugs and selective serotonin reuptake inhibitors with respect to risk of gastrointestinal bleeding has appeared in the literature (56).

Like additive or supra-additive interactions, antagonistic or opposing interactions can occur between two drugs that occupy pharmacologically identical or dissimilar receptors. The ultimate effect is reduced pharmacological activity of one of the interacting drugs. The ability of the narcotic antagonist naloxone to reverse the untoward effects including respiratory depression of a narcotic agonist overdose is an example of a therapeutically beneficial drug interaction occurring at the same receptor subtypes (μ and κ opiate receptors) (89). On the other hand, the ability of even short-term glucocorticoid use to diminish the hypoglycemic effect of various anti-diabetic drugs is an antagonistic interaction that is both undesirable and occurring at distinct receptors.

Adrenergic neuronal interactions

Considering the wide use of epinephrine in outpatient dentistry the adrenergic neuron is a potential site of some clinically significant drug interactions. These interactions can share characteristics of both enzyme-inhibiting and receptor-stimulating or antagonistic interactions. As illustrated in Fig. 2, the key transmitter released from the adrenergic neuron is norepinephrine, which activates predominantly α1 and β1 receptors. Epinephrine administered via local anesthetic injection can activate α1, β1, and β2 receptors. Epinephrine's action is primarily terminated via breakdown by extraneuronal catechol-*O*-methyltransferase and reuptake back into the neuron. Thus potential drug interactions with epinephrine can result with drugs that block either epinephrine's activity at adrenergic receptors, reuptake into the adrenergic neuron or degradation by catechol-*O*-methyltransferase (174, 252). The clinical outcomes of these types of interactions will be discussed later in this paper.

The remainder of this paper will summarize what the authors believe to be important drug interactions as they relate to dentistry that were not covered in detail in earlier sections of this paper. Some reported adverse drug interactions, such as the one between monoamine oxidase inhibitors and epinephrine, while widely promulgated in the literature and drug package inserts, are not supported by scientific fact (252). Other less recognized but recently reported interactions, such as the ability of selective serotonin reuptake inhibitors to enhance the potential for gastrointestinal bleeding among users of non-steroidal anti-inflammatory drug may be especially relevant to providers of dental care.

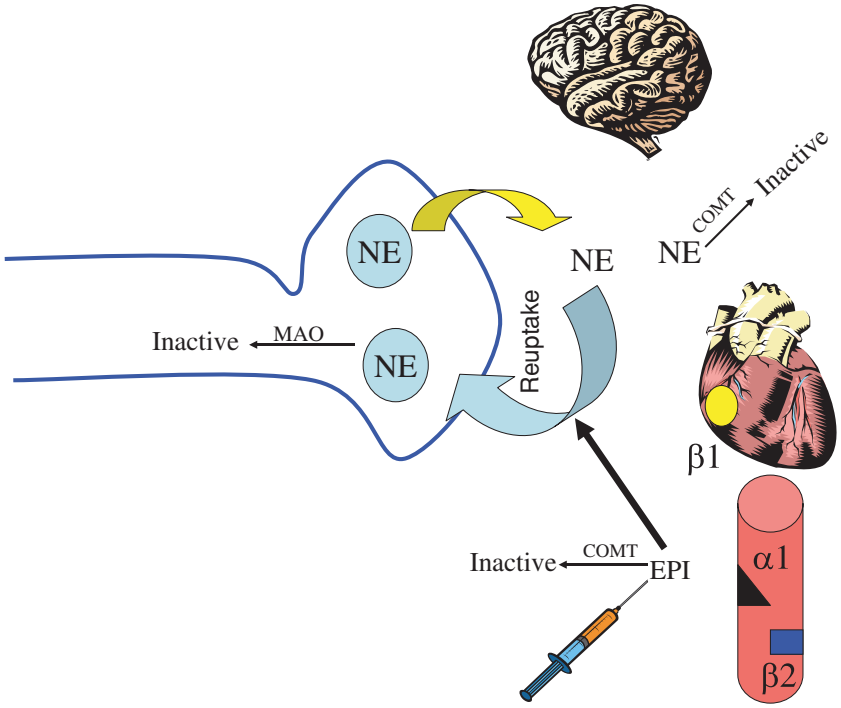

Fig. 2. Simple schematic of the adrenergic neuron with various post-synaptic receptors. Stimulation of alpha-1 adrenergic receptors (α1) leads to vasoconstriction predominantly in the skin and mucous membrane tissues. Stimulation of beta-1 adrenergic receptors (β1) increases heart rate and contraction force. Stimulation of beta-2 adrenergic receptors (β2) leads to vasodilatation predominantly in skeletal muscle and certain internal organ vascular beds. Effects of both endogenous norepinephrine (NE) and injected epinephrine (EPI) can be terminated by catechol-*O*-methyltransferase (COMT) and neuronal reuptake, while NE is also degraded by intraneuronal monoamine oxidase (MAO). Both catecholamines, while present in the central nervous system, do not cross the blood–brain barrier from the periphery.

Adverse interactions involving antibiotic / antifungal agents

The duration of drug therapy with antimicrobial agents, with the exception of single-dose endocarditis and prosthetic joint prophylactic regimens, is generally more prolonged than that of other drug classes used in dentistry. This in itself increases the risk of adverse drug interactions compared to other drug classes (102). Add to this the fact that four commonly used antibiotics in dentistry (clarithromycin, erythromycin, ciprofloxacin, and metronidazole) are potent inhibitors of various cytochrome P450 isoforms (Table 2) and the potential for adverse drug interactions is further increased.

Ciprofloxacin and erythromycin with CYP1A2 substrates

Ciprofloxacin and erythromycin are CYP1A2 isoenzyme inhibitors, thus they can reduce the biotransformation and raise the blood levels of CYP1A2 substrate drugs. Like all cytochrome P450 adverse drug interactions, they are most clinically relevant when the substrate drug is taken orally and possesses a relatively high first-pass effect. The longer one is on the substrate drug, the inhibitor drug, or both drugs, the greater the chance for a clinically meaningful interaction. Table 2 lists some common CYP1A2 substrates and the potential results of the interaction will resemble an overdose of the substrate drug. For example tacrine, a recently approved anti-Alzheimer agent, is an acetylcholinesterase inhibitor, thus increasing acetylcholine concentrations in the central nervous system (the target site) and elsewhere in the body. Excessive blood levels of tacrine induced by concomitant erythromycin or ciprofloxacin therapy could thus be manifested in excessive cholinergic activity at both muscarinic and nicotinic cholinergic receptors, possibly resulting in excessive salivation, lacrimation and sweating, gastrointestinal hypermotility, bradycardia, pupillary constriction, muscle cramps, and central nervous system excitation / agitation (29). Table 3 lists the potential clinical outcomes of coadministration of erythromycin or ciprofloxacin with some CYP1A2 substrates (24, 29, 189, 195, 221, 227, 231, 247).

Metronidazole and fluconazole with CYP2C9 substrates

As shown in Table 2, metronidazole and fluconazole may be involved in drug interactions that relate to their ability to inhibit the CYP2C9 isoenzyme, causing the accumulation of various CYP2C9 substrates. The interaction that is probably most clinically relevant to practicing dentists is the ability of metronidazole to significantly increase the blood concentrations, half-life, and associated hemorrhagic potential of the anticoagulant warfarin (125, 186). In addition, the ability of metronidazole to cause the accumulation of the antiepileptic drug and CYP2C9 substrate phenytoin is supported by at least one well-designed clinical trial (33). Excessive phenytoin blood levels increase the risk of drowsiness, confusion, diplopia,

Table 3. Adverse drug interactions involving erythromycin and ciprofloxacin with some CYP1A2 substrates

CYP1A2 substrates	Potential interaction
Fluvoxamine, imipramine	Substrate accumulation leading to excessive anticholinergic and α1-blocking activity resulting in xerostomia, constipation, elevations in intraocular pressure, tachycardia and other dysrhythmias, sedation, confusion, and orthostatic hypotension.
Theophylline	Substrate accumulation leading to excessive blockade of adenosine receptors and phosphodiesterase resulting in tachycardia and other dysrhythmias, tremors, and seizures
Clozapine, Halperidol	Substrate accumulation leading to excessive anticholinergic, antidopaminergic, and α1-blocking effects leading to xerostomia, constipation, sedation, tachycardia, extrapyramidal effects, orthostatic hypotension, and non-compliance because of these side effects in a population where compliance is already not optimal because of the disease state.
Tacrine	Substrate accumulation leading to excessive cholinergic activity at both muscarinic and nicotinic receptors resulting in excessive salivation, lacrimation, and sweating, diarrhea, miosis, bradycardia, muscle cramping, and central nervous system excitation and agitation.

ataxia, and nystagmus. The antifungal drug fluconazole because of its CYP2C9-inhibiting activity appears to be involved in the same interactions as metronidazole with respect to warfarin and phenytoin (32, 246). Before prescribing metronidazole or fluconazole to dental patients on chronic warfarin or phenytoin therapy, consultation with the prescribing physician is advised. One other potential interaction in this category where the clinical significance is unclear is the ability of fluconazole to diminish the metabolic activation of the CYP2C9 prodrug losartan to its active metabolite E-3174, potentially leading to diminished antihypertensive activity (124).

Erythromycin, clarithromycin, and azole antifungals with CYP3A4 substrates

Of all the cytochrome P450 isoenzymes, CYP3A4 metabolizes the greatest number of drug substrates and correspondingly is involved in the greatest number of potential metabolic drug interactions (Table 2). Interestingly, across a particular drug class, whether it be 'statin' cholesterol-lowering drugs or macrolide antibiotics, not all members equally participate as substrates or enzyme inhibitors with regards to drug interactions. With regards to the statins, lovastatin, simvastatin, and atorvastatin are predominantly metabolized by CYP3A4 while pravastatin is not, accounting for the reduced risk of rhabdomyolysis with pravastatin taken concomitantly with a CYP3A4 enzyme inhibitor compared with statins that are more exclusively CYP3A4 substrates (154, 178, 213). Likewise, while the macrolide antibiotics erythromycin and clarithromycin are potent CYP3A4 isoenzyme inhibitors, azithromycin is not, accounting for the far fewer drug interactions reported with azithromycin than with erythromycin and clarithromycin (98, 153). Compared to erythromycin and clarithromycin, an additional carbon atom around azithromycin's macrocyclic lactone ring probably accounts for its inability to 'tie up' the CYP3A4 isoenzyme (208).

While lidocaine is a CYP3A4 substrate, most clinically significant interactions of this type involve the oral intake of substrates with high first-pass effects, often taken on a chronic basis, accounting for the lack of reported interactions between lidocaine and CYP3A4 isoenzyme inhibitors in the dental setting. However, the ability of erythromycin, clarithromycin, and azole antifungal drugs to inhibit the metabolism of other CYP3A4 substrates is not only clinically significant but has led in some cases to life-threatening outcomes, usually as a result of an extension of the drug substrate's therapeutic and toxic effects (5, 30, 31, 39, 69, 81, 83, 92, 106, 112–114, 121, 123, 130, 131, 134, 139, 140, 144, 154, 178, 179, 183, 199, 218–220, 237, 240, 248). Table 4 lists some of the clinical outcomes of adverse drug interactions between CYP3A4

Table 4. Adverse drug interactions involving erythromycin, clarithromycin and azole antifungal drugs with some CYP3A4 substrates

CYP3A4 substrates	Potential interaction
Astemizole, cisapride, pimozide, terfenadine	Substrate accumulation leading to cardiac QT interval prolongation and torsades de pointes ventricular arrhythmias.
Atorvastatin, cerivastatin, lovastatin, simvastatin	Substrate accumulation leading to diffuse myalgias, rhabdomyolysis, and renal failure caused by blocking of the renal tubule system by skeletal muscle breakdown products
Felodipine, nifedipine and possibly other calcium channel blockers	Substrate accumulation leading to an extension of the drugs' antihypertensive effect resulting in severe hypotension and edema
Cyclosporine, tacrolimus	Substrate accumulation leading to excessive immunosuppression and nephrotoxicity
Warfarin	Substrate accumulation leading to increased prothrombin times, international normalized ratios, and an increased risk of serious bleeding
Carbamazepine	Substrate accumulation leading to increased risk of ataxia, vertigo, drowsiness, and confusion
Alprazolam, diazepam, midazolam, triazolam	Substrate accumulation leading to excessive and prolonged sedation. Increased risk of airway obstruction in the pediatric dental population

substrates and enzyme inhibitors. Of special interest to dentists is the fact that midazolam, a popular oral sedative agent in dentistry (244), is a CYP3A4 substrate and blood levels of even a single dose of this agent can be significantly elevated by a relatively short course of a CYP3A4 isoenzyme inhibitor, resulting in prolonged and excessive central nervous system depression (96, 152, 184). While oral benzodiazepines as a whole have a large therapeutic index, the pediatric dental population appears to be especially vulnerable to the potential outcomes of excessive sedation, most notably airway obstruction, which can be caused by high blood levels of these drugs (50).

Metronidazole and alcoholic beverages

This well-known disulfiram or Antibuse®-like reaction stems from the ability of metronidazole, like disulfiram, to inhibit the enzyme acetaldehyde dehydrogenase in the ethanol degradation pathway, resulting in an accumulation of acetaldehyde in the bloodstream (Fig. 3). While not life-threatening, the drug interaction can produce flushing, headache, nausea, and cardiac palpitations and because of this there were once thoughts of employing chronic metronidazole therapy in the treatment of alcoholics. The interaction is supported by numerous anecdotal reports and several studies with varying rates of occurrence (21, 190, 207). Alcohol consumption should be avoided during metronidazole therapy, and for at least 3 days afterwards.

Clarithromycin, erythromycin, and azithromycin with digoxin

As previously discussed, the importance of P-glycoprotein in the bioavailability of various drug substrates is a growing area of research. The ability of the P-glycoprotein inhibitors clarithromycin and erythromycin to inhibit the extrusion of digoxin from the bloodstream into the intestinal lumen or renal tubular system, has apparently contributed to the rapid rise in digoxin blood levels in several patients resulting in classic digitalis toxicity (202, 243). In addition, the ability of these drugs and azithromycin to inhibit the growth of the intestinal bacterium *Eubacterium lentum*, which metabolizes a large portion of digoxin in approximately 10% of individuals, may contribute to elevated digoxin levels in some patients (171, 228). In light of the extremely low therapeutic index of digoxin, these antibiotics should be avoided in patients on digoxin therapy.

Bactericidal with bacteriostatic antibiotics

Table 5 provides a general listing of some commonly prescribed bactericidal and bacteriostatic antibiotics. Bactericidal antibiotics tend to be most efficacious against actively growing bacteria, so that the concomitant administration of a bacteriostatic agent could in fact produce an antagonistic effect. There are several studies in the literature in which the simultaneous administration of penicillin with either tetracycline or erythromycin was less effective than penicillin alone (141, 185, 221, 223). While combinations of bactericidal and bacteriostatic agents have on occasion been successfully employed to prevent the emergence of resistant strains of *Helicobacter pylori* infections of the gastrointestinal tract (95, 256), there is no rationale for these combinations in the treatment of odontogenic infections. The combinations are likely to lead to greater toxicity than monotherapy and, at least with penicillins, a diminution of antibiotic effectiveness.

Antibiotics and oral contraceptives

Certainly one of the most debated interactions with respect to validity is the reported ability of commonly prescribed antibiotic agents to reduce blood levels and effectiveness of oral contraceptive agents (65, 102). In reality, while case reports of oral contraceptive failure, defined as pregnancy or ovulation, following antibiotic therapy with penicillins, tetracyclines, metronidazole, erythromycin, and cephalosporins have appeared in the literature (9, 16, 20, 66, 72, 73) all clinical studies to date with these or related agents have failed to demonstrate a clinically or statistically significant reduction in contraceptive blood levels or efficacy (8, 11, 12, 100, 122, 148, 173, 176, 187).

As shown in Table 2, both the estrogen and progestin components of the typical combination oral contraceptive pill are CYP3A4 substrates, and thus

Fig. 3. Metabolic pathway of alcohol detoxification. Metronidazole, like disulfiram, blocks the enzyme acetaldehyde dehydrogenase, causing an accumulation of acetaldehyde and the accompanying disulfiram-like effect.

Table 5. Grouping of antibiotics by bactericidal and bacteriostatic categories

Bacteriostatic	Bactericidal
Tetracyclines	Penicillins
Erythromycin	Cephalosporins
Clarithromycin	Metronidazole
Azithromycin	Ciprofloxacin
Clindamycin	Aminoglycosides
Sulfonamides	

the ability of the antituberculosis drug rifampin and its analogue rifabutin, both potent inducers of the CYP3A4 isoform, to significantly reduce blood levels of the contraceptive is in fact not surprising and well supported by clinical trials (6, 22). However, none of the antibiotics commonly employed in dentistry upregulate this enzyme. In fact erythromycin and clarithromycin inhibit this enzyme and one clinical trial demonstrated that the latter increased oral contraceptive blood levels (12). In trying to develop a plausible mechanism for sporadic reports of oral contraceptive failure, the ability of common antibiotics to inhibit the enterohepatic recirculation of the estrogen steroid component of the pill (usually either ethinylestradiol or mestranol) is the most popular (7, 65). As shown in Fig. 4, the theory assumes that in a small number of women, a significant portion of the estrogen molecule undergoes both pre-hepatic and hepatic metabolic inactivation reactions before absorption into the bloodstream. In the absence of antibiotic therapy, normal gut flora would then cleave the glucuronic acid or sulfate groups that were added, liberating the lipid-soluble and active parent estrogen molecule that can be reabsorbed into the portal circulation. With antibiotics on board, the normal gut flora would be reduced, resulting in a significant portion of the metabolized estrogen molecules remaining in this state and lost to excretion. Estrogen blood levels would then fall, restoring the female's ability to ovulate.

While pooled data published in clinical studies have never shown a statistically significant reduction in estrogen levels during common antibiotic therapy when compared to control levels in oral contraceptive users, a few individual women on these studies have demonstrated dramatic decreases while on antibiotics (70). For example in one study by Back et al. (8) involving seven women, the overall analysis revealed no statistical differences in ethinylestradiol levels while taking ampicillin and after the discontinuation of antibiotic therapy approximately 1 month later. However, two of these women exhibited 30% and 90% reductions of ethinylestradiol levels, respectively, while on ampicillin. Whether these individual differences simply reflect the often wide variations in oral absorption of these drugs (10), or represent a potential rare interaction in a subset of women who depend greatly on enterohepatic recirculation in maintaining therapeutic blood levels of the anti-ovulatory steroid is unknown. Although the overall failure rate of oral contraceptives during common antibiotic therapy may be no greater than when taking oral contraceptives alone, advising female patients about the potential for a rare interaction and to use additional barrier methods of contraception (while continuing to take their oral contraceptives) during antibiotic therapy and for at least 1 week beyond the last antibiotic dose still appears prudent (65, 70).

Interactions involving analgesic agents

In the typical dental or periodontal practice, while the use of analgesics is widespread, serious adverse drug interactions involving these agents are rarely reported probably because of the short-term duration of analgesic therapy and the relatively low daily doses that are most often prescribed (107, 166). However, there are a number of potential adverse drug inter-

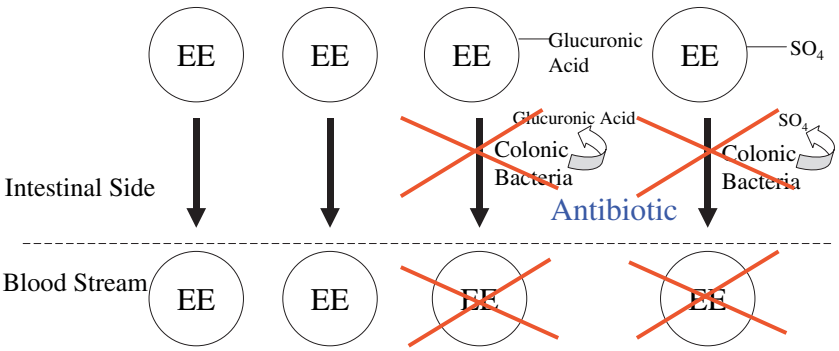

Fig. 4. Proposed enterohepatic recirculation of ethinylestradiol (EE) inhibited by antibiotic therapy. By either killing or inhibiting the growth of enteric bacteria, the reactivation of the parent estrogen molecule would be blocked leading to diminished blood levels and reduced anti-ovulatory activity.

actions involving this class of drugs of which the clinician should be aware, some involving other drugs with low therapeutic indices and others, just recently appearing in the literature.

Acetaminophen with ethanol

In addition to being the most widely sold over-the-counter analgesic in the United States, the number of prescriptions dispensed for acetaminophen–narcotic combination drugs containing hydrocodone, propoxyphene, codeine, and oxycodone were ranked 1st, 24th, 32nd, and 43rd, respectively, of all prescription medications in 2005 (229). Maximum daily doses of acetaminophen should not exceed 4,000 mg. Hepatotoxicity is a complication of both chronic alcohol abuse and acute overdoses of acetaminophen. As illustrated in Fig. 5, more than 95% of a therapeutic dose of acetaminophen eventually undergoes glucuronidation or sulfation in the liver, essentially inactivating the molecule. Approximately 4% of the parent compound is a substrate for CYP2E1, and is converted to a potentially highly reactive hepatotoxic metabolite known as *N*-acetyl-para-benzoquinonemine (205). However, in healthy individuals the relatively small amount of *N*-acetyl-para-benzoquinonemine that is formed is rapidly inactivated by combining with glutathione in the liver and other tissues (97). In an acute overdose of acetaminophen, typically 15 g or more, the glucuronidation pathway becomes saturated allowing far more acetaminophen to be processed by CYP2E1 and resulting in an excessive formation of *N*-acetyl-para-benzoquinonemine that overwhelms the body's natural glutathione stores (205).

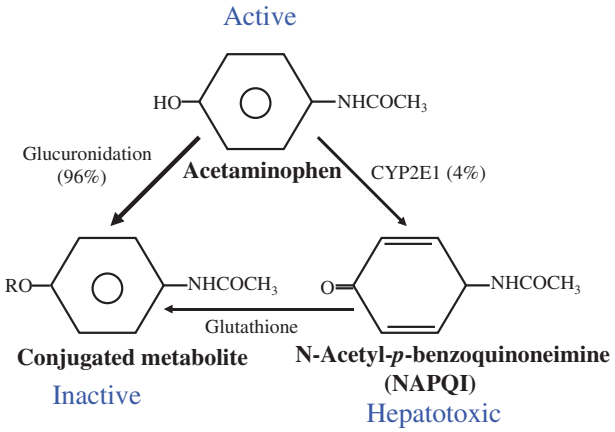

Fig. 5. Typical biotransformation of acetaminophen when taken at therapeutic doses. The addition of glucuronic acid represented by an 'R' inactivates approximately 96% of the acetaminophen molecules while approximately 4% is converted to the potentially hepatotoxic metabolite *N*-acetyl-para-benzoquinonemine via CYP2E1, which in turn is rapidly inactivated by glutathione.

The theoretical problem with alcohol plus even high therapeutic doses of acetaminophen is that alcohol is an inducer of CYP2E1 (Table 2) and could increase the levels of *N*-acetyl-para-benzoquinonemine that are formed. What makes the interaction so complex is that alcohol is also a substrate for CYP2E1, and when both alcohol and acetaminophen are on board simultaneously, it is the alcohol that preferentially occupies the isoenzyme, possibly explaining why in some instances massive acute overdoses of acetaminophen did not produce the expected hepatotoxicity in subjects who also consumed alcohol (216). Concern has been voiced that subjects that are potentially most at risk for hepatotoxic outcomes are frequent 'social drinkers', who stop drinking and within a short time start consuming high therapeutic doses or supratherapeutic doses of acetaminophen. CYP2E1 could remain upregulated for at least a few weeks, but now acetaminophen would be occupying the enzyme and not alcohol (97). Warnings appear on the label of all acetaminophen-containing products cautioning of the risk of increased hepatotoxicity with the consumption of three or more drinks per day. Alcoholics carry the additional burden of reduced amounts of a protein transporter that carries glutathione to the mitochondria of the hepatocytes, possibly putting them at greater risk for hepatotoxicity than non-alcoholics, especially in an overdose situation (205). While a daily dosage maximum of 2 g acetaminophen is recommended for alcoholics, it is interesting to note that well-designed clinical trials or case control studies reveal little toxicity of the combination in this population, as long as the acetaminophen dose remains in the therapeutic range (58, 205).

Interactions with non-steroidal anti-inflammatory drugs

Some common non-steroidal anti-inflammatory drugs employed in the management of acute pain are illustrated in Table 6. They are grouped as being non-selective cyclooxygenase inhibitors, that is they inhibit cyclooxygenase-1 at least as readily as, if not more so than, they inhibit cyclooxygenase-2, semi-selective cyclooxygenase-2 inhibitors (meaning that they are two- to three-fold more selective in blocking cyclooxygenase-2 over cyclooxygenase-1), or highly selective cyclooxygenase-2 inhibitors (meaning that they are seven-fold or more selective in their cyclooxygenase-2 blocking activity) (105).

Table 6. Some commonly prescribed non-steroidal anti-inflammatory drugs in the dental setting

Non-selective cyclooxygenase inhibitors	Semiselective cyclooxygenase-2 inhibitors	Highly selective cyclooxygenase-2 inhibitors
Aspirin	Diclofenac	Celecoxib
Diflunisal	Etodolac	Etoricoxib*
Ibuprofen	Meloxicam	Lumiracoxib*
Ketoprofen		Rofecoxib†
Naproxen		Valdecoxib†

*Available in Europe.
†Removed from worldwide marketplace.

Aspirin is unique among non-selective non-steroidal anti-inflammatory drugs because it irreversibly acetylates cyclooxygenase-1 in the platelet, the major reason for its cardioprotectant use (107). Several of the selective cyclooxygenase-2 inhibitors have been removed from the worldwide marketplace because of increased cardiovascular risk and additional scrutiny in this area is underway by regulatory agencies for all non-steroidal anti-inflammatory drugs (105). Some interactions involving non-steroidal anti-inflammatory drugs with lithium, anticoagulants, and oral hypoglycemics have already been discussed in earlier sections of this paper. The following sections will focus on adverse interactions involving non-steroidal anti-inflammatory drugs with other groups of drugs.

Non-steroidal anti-inflammatory drugs and ethanol

The combined use of alcohol and non-steroidal anti-inflammatory drugs significantly increases the risk of fecal blood loss associated with gastrointestinal erosions and ulcers (94). Not only are both alcohol and non-steroidal anti-inflammatory drugs (especially non-selective cyclooxygenase-inhibiting non-steroidal anti-inflammatory drugs) capable of damaging the gastrointestinal mucosa, but alcohol may also stimulate gastric acid secretion, aggravating the gastrointestinal toxicity of non-steroidal anti-inflammatory drugs. It has been recommended that aspirin and alcohol consumption be separated by at least 12 hours (97). Probably the short course of analgesic therapy after routine dental procedures limits the severity of this interaction in dental outpatients. However, warnings appear on the labels of all non-steroidal anti-inflammatory drugs containing products of enhanced gastrointestinal toxicity in combination with alcohol if three or more drinks per day are consumed (107).

Non-steroidal anti-inflammatory drugs and antihypertensive drugs

Both cyclooxygenase-1 and cyclooxygenase-2 play important roles in renal homeostasis, specifically in producing vasodilatory prostaglandins that increase renal blood flow and the subsequent excretion of water and sodium (36, 105). In particular, the antihypertensive effects of β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, and diuretics seem to be especially dependent on these prostaglandin mechanisms (117). While aspirin appears devoid of the interaction, other non-steroidal anti-inflammatory drugs including ibuprofen, naproxen, and highly selective cyclooxygenase-2 inhibitors have been shown to at least partially attenuate the blood-pressure-lowering effects of these antihypertensive agents by blocking the synthesis of prostaglandins in the kidney (1, 105, 156, 194, 196). Usually more than 5 days worth of non-steroidal anti-inflammatory drug therapy are necessary before this effect is observed.

Non-steroidal anti-inflammatory drugs with methotrexate

As discussed previously in this paper, methotrexate is a drug with a relatively low therapeutic index. It is administered at relatively high doses with potential side effects of thrombocytopenia, neutropenia, acute renal failure, and mucositis in the treatment of cancer and at lower dosages accompanied by a much better side effect profile in the treatment of rheumatoid arthritis and other conditions requiring immunosuppression (107). With high-dose methotrexate therapy, concomitant non-steroidal anti-inflammatory drugs appear to increase the risk of serious methotrexate side effects, possibly because of a decrease in prostaglandin-dependent renal perfusion and subsequent elimination of methotrexate (86, 230). In rheumatoid arthritis patients taking low-dose methotrexate therapy, non-steroidal anti-inflammatory drugs are often given concomitantly, especially early in therapy, to provide symptomatic relief of joint pain. Dental clinicians are advised not to prescribe additional non-steroidal anti-inflammatory drugs for postoperative pain to these patients or to those consuming non-steroidal anti-inflammatory drugs for other arthritic conditions because additive gastrointestinal or renal toxicity is likely to occur (97).

Non-steroidal anti-inflammatory drugs and selective serotonin reuptake inhibitors

As previously stated, five of the selective serotonin reuptake inhibitors, namely citalopram (Celexa®), S-citalopram (Lexapro®), fluoxetine (Prozac®), paroxitene (Paxil®), and sertraline (Zoloft®), are currently in the top 100 prescribed drugs in the United States (Table 7). They have replaced the older tricyclic antidepressant drugs like imipramine (Tofranil®) as being the initial drugs of choice for treating depression and a variety of affective disorders because of their better side effect profile (56). Over the last 10 years there have been numerous reports of what typically are minor bleeding episodes, such as bruising, epitaxis, and hematoma formation, which resolve after discontinuation of selective serotonin reuptake inhibitor therapy (211). Of special note to periodontal surgeons and other dental surgical specialties is that there are also reports of increased postoperative bleeding in patients taking these drugs (211). In addition, potentially serious upper gastrointestinal bleeding has been reported with the intake of these drugs with population cohort studies reporting odds ratios of 3.0–3.4, meaning the risk of a gastrointestinal bleed is increased at least three-fold in patients taking these drugs compared to the general population (56, 61).

Like neurons in the central nervous system, platelets possess a serotonin reuptake pump and also serotonin receptors (142, 211). Being enucleated and unable to synthesize serotonin, the reuptake process of serotonin from the bloodstream is crucial for storage of this chemical in the platelet. Release of this stored serotonin plays an important role in platelet aggregation. As they do in central nervous system neurons, selective serotonin reuptake inhibitors block the reuptake of serotonin into the platelet and also cause a downregulation of serotonin receptors on the platelet's outer surface (211). Both of these events may contribute to the ability of selective serotonin reuptake inhibitors to decrease platelet function and enhance bleeding risk.

It is well known that non-steroidal anti-inflammatory drugs, especially when taken chronically, also increase gastrointestinal bleeding risk by an inhibition of cyclooxygenase-1 in the platelet and on the gastrointestinal mucosa (107). Pooled published odds ratios of this increased risk compared to non-users of non-steroidal anti-inflammatory drugs are in the 3.7–4.5 range (61, 136), with certain individual drugs, such as ibuprofen and highly selective cyclooxygenase-2 inhibitors, below these ranges and others, such as ketoprofen, with odds ratios that are much higher (110, 136). When selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs are taken concurrently the pooled odds ratios for an upper gastrointestinal bleed dramatically increase to between 15.6 and 16.7 (56, 61). Surrogate measures of anti-ulcer and anti-gastritis drug consumption also increase in the population consuming concomitant non-steroidal anti-inflammatory drugs and selective serotonin reuptake inhibitors with a reported odds ratio of 12.4 (63). This interaction appears to be greater than a simple additive effect of each individual drug class.

While not explored in clinical trials, an additional factor involved in this interaction might be the ability of certain selective serotonin reuptake inhibitors to inhibit the metabolism of certain non-steroidal anti-inflammatory drugs. As shown in Table 2, fluvoxamine, paroxitene, and sertraline are CYP2C9 isoenzyme inhibitors while diclofenac, ibuprofen, and naproxen are substrates for the same cytochrome P450 isoenzyme. While the significance of this interaction with the short-term use of non-steroidal anti-inflammatory drugs for control of postoperative dental pain in the patient population taking selective serotonin reuptake inhibitor is unknown, the combination could result in increased postoperative bleeding. In addition, clinicians treating chronic orofacial pain in their practice, where more prolonged trials of one or both drug types can be

Table 7. Pharmacological grouping of various antidepressants with common trade names in parentheses

Tricyclic antidepressants	Monoamine oxidase inhibitors	Selective serotonin reuptake inhibitors
Amitriptyline (Elavil®)	Isocarboxazid (Marplan®)	Fluoxitene (Prozac®)
Desipramine (Norpramin®)	Phenelzine (Nardil®)	Paroxitene (Paxil®)
Doxepin (Sinequan®)	Tranylcypromine (Parnate®)	Sertraline (Zoloft®)
Imipramine (Tofranil®)	Selegiline (Eldepryl®)*	Citalopram (Celexa®)
Protrptyline (Concordin®)		S-Citalopram (Lexapro®)

*Employed in the treatment of Parkinson's disease.

contemplated, are advised to avoid the combination. Older tricyclic antidepressants, which anecdotally appear to be generally more efficacious in the chronic orofacial pain population, do not appear to have as great a gastrointestinal bleeding risk when combined with non-steroidal anti-inflammatory drugs, although this assumption needs to be further evaluated (56, 63).

Non-steroidal anti-inflammatory drugs and cardioprotective doses of aspirin

Low-dose aspirin (75–325 mg/day) has various antiplatelet indications including prevention of second myocardial infarction, unstable angina pectoris, prevention of thrombotic events after coronary artery bypass or stenting procedures, and the prevention of cardiovascular events in so called high-risk individuals (88, 107). In reality although the drug is being bought over-the-counter for these purposes, these really represent prescription uses of aspirin (107). The unique ability of aspirin to irreversibly acetylate cyclooxygenase-1 in the platelet makes it an ideal drug for cardioprotection.

Unlike aspirin, the blockade of cyclooxygenase-1 by non-selective non-steroidal anti-inflammatory drugs, such as ibuprofen and naproxen, is reversible. Theoretically, with both aspirin and a non-selective non-steroidal anti-inflammatory drug on board at the same time, drugs like ibuprofen could compete with aspirin for the cyclooxygenase-1 binding site in the platelet (41). Because ibuprofen's antiplatelet effect is temporary and aspirin not bound to cyclooxygenase-1 will be rapidly biotransformed to salicylic acid, which like ibuprofen is only a reversible inhibitor of cyclooxygenase, the combination of the two drugs could reduce the antiplatelet activity of aspirin. A clinical study by Garret FitzGerald's group demonstrated that in aspirin-naïve individuals, the intake of 400 mg ibuprofen 2 hours before the intake of 81 mg aspirin each morning for 6 days, greatly attenuated the antiplatelet activity of aspirin (41). The percent inhibition of serum thromboxane B_2 activity, a surrogate marker of platelet inactivation, fell from 98–99% inhibition to less than 50% inhibition, 24 hours after the aspirin dose when ibuprofen was taken before aspirin. This correlated to a direct reduction in the antiplatelet activity of aspirin. When subjects took the drugs in the reverse order, that is low-dose aspirin before ibuprofen, thromboxane inhibition remained greater than 98%. Rofecoxib and acetaminophen, no matter in what order they were given in relation to aspirin, had no effect on the ability of aspirin to inhibit thromboxane synthesis and platelet aggregation. This lack of effect is because the highly selective cyclooxygenase-2 inhibitors and acetaminophen have little effect on cyclooxygenase-1 in the platelet. When 81 mg aspirin was followed by three doses of ibuprofen of 400 mg each for 6 days, serum thromboxane B_2 inhibition by aspirin was reduced to about 70% of maximum, whereas the semiselective cyclooxygenase-2 inhibitor diclofenac maintained thromboxane inhibition at 92%. A greater than 90% inhibition of thromboxane B_2 concentrations is thought to be needed for a nearly complete inhibition of platelet aggregation and resulting cardioprotective activity (80, 201).

While the results of the above study are intriguing they do not represent the typical scenario that would be seen in dental outpatients requiring an analgesic for acute pain; that is the patients would already have been on cardioprotective doses of aspirin for a significant amount of time and then a non-steroidal anti-inflammatory drug would be prescribed for short-term pain relief. In a clinical study that more closely followed this 'real-life scenario' subjects were given 81 mg aspirin once per day for 8 days and then were randomized to receive ibuprofen 400 mg or placebo three times a day plus morning aspirin for an additional 10 days (53). During the 10 days of ibuprofen or placebo treatments, serum thromboxane B_2 inhibition averaged between 97.5 and 99.1% in the ibuprofen group and between 98.6 and 98.8% in the placebo group. Therefore, under the conditions of this trial, which more closely resembles that of a typical dental outpatient on cardioprotective aspirin therapy, the antiplatelet activity of aspirin was preserved with concomitant ibuprofen administration. Additional factors that need to be investigated in the future include potential interactions of low-dose aspirin with other non-steroidal anti-inflammatory drugs, any effect of higher daily doses of ibuprofen (>1,200 mg) and other non-steroidal anti-inflammatory drugs, and also the effect, if any, of the aspirin formulation itself, whether it be immediate release or enteric coated.

Interactions with narcotic analgesic agents

In the treatment of acute pain in the outpatient dental setting, combining minimally effective doses of narcotic analgesics (60 mg codeine, 10 mg hydrocodone, 5 mg oxycodone, 75 mg tramadol, 100 mg propoxyphene) with optimal or near optimal doses of

aspirin or acetaminophen (600–1,000 mg) will usually provide better analgesia with fewer side effects than simply administering a higher dose of the narcotic alone (27, 157). For more severe postoperative pain, narcotic combinations with ibuprofen are also rational as long as the ibuprofen dose is near optimal, that is 400 mg (67, 236). Narcotics are central nervous system depressants binding to various opiate receptor subtypes in the brain, spinal cord and periphery (89). Therefore as previously discussed, the administration of any narcotic analgesic agent in the presence of another central nervous system depressant such as alcohol, benzodiazepines or barbiturates can lead to additive or supra-additive central nervous system depression including excessive psychomotor impairment, sedation, and unconsciousness (97). Of special concern to pediatric dentists is the potential additive or supra-additive effects of high-dose narcotic sedatives with local anesthetics in children; this potentially life-threatening interaction is discussed later in this paper in the section on local anesthetic interactions. Additional adverse drug interactions involving narcotic agents are discussed below.

Codeine and tramadol with CYP2D6 inhibitors

Codeine and tramadol are CYP2D6 substrates and are prodrugs, or at the very least depend significantly on their metabolic activation by CYP2D6 for their ultimate analgesic effect. In the case of codeine, the parent compound is essentially devoid of analgesic activity but its active demethylated metabolite morphine accounts for most of the effect (68). In the case of tramadol, the parent molecule, which is made up of two isomers, (+) and (–), appears to possess analgesic activity by enhancing noradrenergic and serotonergic activity in the central nervous system, with the (+) demethylated metabolite, *O*-demethyl tramadol, also known as M1, contributing additional analgesic activity though opiate receptor activation (77, 138). Because of this reliance on CYP2D6 activation for both drugs, pharmacokinetic drug interactions with CYP2D6 inhibitors could result in a reduction in their analgesic effects (106). It has been demonstrated with both codeine and tramadol that the administration of the antiarrhythmic agent quinidine, a known CYP2D6 inhibitor, essentially abolishes their analgesic activity (68, 87, 215). Probably even more relevant to practicing dentists is that other much more widely prescribed CYP2D6 inhibitors include the selective serotonin reuptake inhibitors fluoxetine, paroxitene, and sertraline (Table 2); all having the theoretical potential to diminish the analgesic activity of codeine and tramadol. The clinical significance of this possibility needs to be explored. Furthermore, the contribution of CYP2D6 activation of hydrocodone to hydromorphone, and of oxycodone to oxymorphone in the overall analgesic activity of these commonly prescribed drugs, and the effects of CYP2D6 inhibition on this process is currently unknown (225).

Meperidine, tramadol, and propoxyphene with monoamine oxidase inhibitors

Meperidine is a synthetic narcotic derivative that was more popular in the past as a component of intravenous conscious sedation regimens (103) and is still employed orally in pediatric sedation regimens and occasionally as a single entity analgesic agent in outpatient dentistry (170, 244). In reality, for postoperative pain, there is no good reason to employ meperidine, or indeed any single-entity narcotic, that is not combined with acetaminophen, aspirin or ibuprofen in the vast majority of dental patients. Clearly, study after study reveals that oral narcotics alone at what are considered therapeutic doses, are no better than and often inferior to therapeutic doses of aspirin, acetaminophen, and ibuprofen, and account for the majority of side effects that are observed in clinical trials (26, 51, 52). In addition, the extremely high first-pass effect of meperidine makes oral dosing with this agent extremely unpredictable (67).

Equally as problematic with meperidine is that on overdose, in addition to the classic opioid-induced central nervous system depression signs, a serotonin-like syndrome manifested by tremors, convulsions, muscle rigidity, and hyperexia can also occur as the result of an accumulation of meperidine's neurotoxic metabolite normeperidine (89, 221). Monoamine oxidase inhibitors (Table 7), including phenelzine, tranylcypromine, isocarboxazid, and selegiline, are employed in the treatment of depression and more recently in the treatment of Parkinson's disease. They exacerbate the untoward effects of normeperidine possibly by inhibiting the inactivation of this neurotoxic meperidine metabolite by monoamine oxidase. Serious and potentially life-threatening events have been reported in monoamine oxidase inhibitor consumers with even therapeutic doses of meperidine (64, 221, 257). Similar to meperidine, other opioids in the phenylpiperidine series, including tramadol and propoxyphene, possibly because of their own

intrinsic serotonergic activity, have been reported to also produce a serotonin-like syndrome when taken concurrently with monoamine oxidase inhibitors (90). Therefore meperidine, tramadol, and propoxyphene must be absolutely avoided in patients on monoamine oxidase inhibitors.

Adverse drug interactions associated with sedatives and anxiolytics

Orally administered sedative and anxiolytic drugs, administered for patient relaxation and relief of anxiety, are valuable additions to a dentist's pain control armamentarium. In general, the most significant systemic adverse drug reactions associated with these agents are signs of excessive central nervous system depression: prolonged sedation, lethargy, loss of consciousness, and/or respiratory depression. Drug interactions associated with sedative and anxiolytic drugs used in dentistry are summarized in Table 8. Some of the most serious interactions have been previously introduced: the inhibition of benzodiazepine drug metabolism induced by macrolide antibiotics and 'azole' antifungal agents, combinations of opioid analgesics and other central nervous system depressants, and the interaction between meperidine and monoamine oxidase inhibitors.

Summation drug interactions

Combining two or more central nervous system depressant drugs will predictably result in increased levels of central nervous system depression. This summation reaction is the basis for many useful drug combinations in dental therapeutics, such as multidrug intravenous sedation in adults and oral sedative therapies in children (71, 165, 169, 222). The use of combinations of central nervous system drugs may also increase the risk of unexpected oversedation and respiratory depression, particularly if opioids are included in the regimen (76, 161).

Because of the possible severe consequences that may occur with the combination of central nervous system depressants, dentists routinely inform patients to restrict alcohol consumption following sedation procedures or when taking centrally-acting opioid analgesics postoperatively. Alcohol consumption following sedation therapy should be restricted because severe drowsiness and significant impairment of psychomotor performance, including driving skills, can occur. Summation reactions associated

Table 8. Adverse drug interactions with sedatives and anxiolytics

A. Summation interactions with central nervous system depressants
Examples: codeine and alcohol; or antihistamines and barbiturates
In combination, central nervous system depression is additive for sedatives and/or anxiolytics; loss of consciousness, respiratory depression and death are possible complications
B. Benzodiazepine interactions
Drugs increasing rate of metabolism (i.e. rifampin, carbamazepine)
With increased metabolism, one will see a significant reduction in bioavailability and a decreased sedative response when administering triazolam and oral midazolam
Drugs decreasing rate of metabolism (i.e. cimetidine, erythromycin, indinavir)
A marked increase in bioavailability is seen with triazolam and oral midazolam. Increased depth of sedation and prolonged recovery are likely
C. Barbiturate interactions
Example: warfarin and phenobarbital
Bleeding risk increases when chronic barbiturate therapy is discontinued and warfarin metabolism returns to its normal rate
D. Chloral hydrate interactions
Example: alcohol and chloral hydrate
Each drug limits the metabolism of the other; central nervous system depression is greater than additive
Example: warfarin and chloral hydrate
Competition for plasma protein binding of anticoagulant may cause a higher percentage of unbound warfarin and subsequent hypoprothrombinemia

with alcohol, sedatives or anxiolytics, have also been demonstrated following oral diazepam (132, 145) and sedative antihistamines such as diphenhydramine and promethazine (49, 135, 155, 217).

Benzodiazepine drug interactions

The popularity of the benzodiazepines for oral sedation is a consequence of their large margin of safety and their ability to provide anxiolysis (relief of anxiety) without producing apparent sedation and ataxia. There are numerous agents available that differ primarily in their rates of onset and elimination. Commonly used oral benzodiazepines in dentistry include diazepam (Valium®), triazolam (Halcion®), lorazepam (Ativan®), alprazolam (Xanax®), and oxazepam (Serax®). Midazolam (Versed®), administered intravenously for conscious sedation, is now available as an oral formulation in the United States. With the exceptions of lorazepam and oxazepam, these benzodiazepines are metabolized by hepatic oxidative enzymes. The resulting oxidative metabolites, some of which retain anxiolytic activity, are then conjugated and eliminated primarily through renal excretion (164).

Variable rates of absorption, distribution, and metabolism are reported following orally administered benzodiazepines. Fortunately the therapeutic indices for benzodiazepines are so large that the wide range of dosing recommendations and blood concentrations that have been reported do not significantly impact their safety and efficacy. Minor shifts in elimination are unlikely to result in a drug overdose. The range of plasma concentrations of diazepam has been reported to range from 20 to 260 μg/ml 3 hours after a 15-mg oral dose (150). A drug interaction that causes a 20% increase in diazepam blood concentrations is unlikely to induce significant toxicity. Most healthy patients can tolerate the small variations in a benzodiazepine's absorption or metabolism that may occur when co-administered with an interacting drug. However, clinically significant adverse drug interactions resulting from large alterations in the pharmacokinetics and pharmacodynamics of benzodiazepines have been reported.

The calcium-channel blockers verapamil (Calan®) and diltiazem (Cardizem®) are popular cardiovascular agents used for the management of angina, arrhythmias, and hypertension. Both agents have been shown to inhibit the CYP3A4 isoenzymes required for the metabolism of triazolam and oral midazolam (Table 2). In controlled clinical trials, a 2-day regimen of these calcium-channel blockers decreased the metabolism of midazolam and triazolam and increased the bioavailability of these benzodiazepines when administered orally. Peak blood concentrations have been reported to increase two- to three-fold (13, 239). Similarly, cimetidine (Tagamet®) may inhibit CYP3A4 oxidative metabolism of diazepam, triazolam, and alprazolam. Half-life increases of 30–63% have been reported (4, 79, 206). Elevations of these benzodiazepine blood concentrations would be associated with increased sedation and psychomotor performance deficits. Caution and avoidance of these combinations are recommended, particularly in elderly populations known to be sensitive to benzodiazepines.

The important pharmacokinetic drug interactions associated with erythromycin, clarithromycin, ciprofloxacin, and the azole antifungals such as ketoconazole and itraconazole have been described previously. Because these antimicrobials are potential inhibitors of pre-hepatic and hepatic enzymes required for the metabolism of triazolam and oral midazolam, clinically significant interactions are possible. By decreasing the first-pass effect and improving bioavailability, peak triazolam blood concentrations may increase three-fold (238).

Protease inhibitors, such as indinavir, ritonavir, and nelfinavir, are antiviral agents used in the management of HIV infections. They bind to the active site of the HIV protease enzyme and interrupt the maturation process of newly formed viral particles. These antiviral agents are also capable of inhibiting the CYP3A4 hepatic oxidative enzymes required for the metabolism and elimination of triazolam, alprazolam, and oral midazolam (Table 2). Severe central nervous system and respiratory depression have been reported with the combination (109).

Chronic therapy with the antituberculosis agent rifampin can induce the metabolic enzymes of the gut wall and liver that are responsible for the metabolism of diazepam, midazolam, and triazolam. It has been demonstrated that the bioavailability of oral midazolam is reduced by as much as 96% (14). Triazolam is so rapidly and completely metabolized in the gut before absorption that peak plasma concentrations are only 12% of normal (242). This interaction is one of the most pronounced alterations in drug kinetics ever reported with almost complete loss of triazolam and oral midazolam bioavailability. The subsequent loss of efficacy is quite significant and warrants the use of an alternative sedative such as oral oxazepam or inhalational N_2O.

Similarly, the anticonvulsant carbamazepine (Tegretol®) can induce hepatic enzymes for the

oxidative metabolism of certain benzodiazepines: alprazolam, triazolam, and midazolam (15, 221). Decreased benzodiazepine plasma concentrations and greatly reduced sedative effects may occur after oral administration of these agents. Benzodiazepines that are metabolized through glucuronidation such as oxazepam (Serax®) are suitable alternative agents for sedation.

Barbiturate drug interactions

The use of barbiturates for sedation in dentistry has been greatly curtailed since the introduction of benzodiazepines. Compared to the currently available benzodiazepines, barbiturates are less specific in providing relief of the fear and anxiety associated with dental procedures. Drowsiness and ataxia are frequent side effects of barbiturate sedation. Other disadvantages of barbiturates include a small margin of safety, the induction of hepatic microsomal oxidative enzymes that can alter other drug therapy and their liability for abuse.

Valproic acid (Depakene®) is an antiepileptic drug introduced in 1978 for the management of various partial and generalized seizures. When administered in combination, valproic acid has been shown to reduce the metabolism of phenobarbital, changing its half-life from 96 to 142 hours (62). A delay in the elimination of phenobarbital would result in enhancement and prolongation of sedative effects. Oral benzodiazepines that provide effective sedation and anxiolysis are an appropriate alternative.

When a barbiturate is chronically administered to patients taking warfarin (Dicumarol®), warfarin doses may need to be increased by as much as 30% to maintain therapeutic prothrombin times. The greatest concern for an adverse drug interaction occurs when prolonged barbiturate therapy is discontinued and the enhanced rate of metabolism of warfarin returns to normal. As anticoagulant concentrations subsequently increase, there is a risk of a serious bleeding episode (54). There is little evidence that a single dose of a barbiturate will cause significant induction of hepatic enzymes.

Chloral hydrate interactions

Chloral hydrate, an oral sedative commonly used for sedation of preschool children in pediatric dentistry, has been implicated in a variety of drug interactions. As indicated in the previous section, when administered with other sedatives, chloral hydrate may additively increase levels of central nervous system depression. This interaction may permit practitioners to decrease the doses of both central nervous system depressants and therefore limit the side effects of the individual drugs (116). Similarly, the use of N_2O in combination with chloral hydrate may improve the level of sedation. However, this therapeutic advantage may be lost when N_2O is used in combination with higher doses of chloral hydrate because central nervous system depression may be increased to such an extent that the child's protective reflexes become compromised (169).

Beyond summation of central nervous system depressant effects the combination of chloral hydrate with alcohol produces a supra-additive drug interaction through an alteration of alcohol metabolism. Chloral hydrate and its primary metabolite trichloroethanol competitively inhibit alcohol-metabolizing dehydrogenases, thereby elevating alcohol blood concentrations (210). This combination, commonly known as a 'Mickey Finn' or 'knock-out drops', can induce severe alcohol intoxication with stupor, coma, or death.

As presented in the introductory discussion of drug displacement interactions, chloral hydrate has also been implicated in modifying responses to the oral anticoagulant sodium warfarin. Its secondary metabolite trichloroacetic acid is a potential protein-binding displacing drug, and may significantly increase free warfarin plasma concentrations and its associated bleeding risks.

Adverse drug interactions associated with local anesthetics

This section describes the adverse drug interactions associated with local anesthetics as used for routine dental therapeutics. The amide local anesthetics most commonly used in dentistry, lidocaine, prilocaine, mepivacaine, articaine, and bupivacaine, are essential for providing pain-free dental services. Conservative weight-based dosage guidelines for local anesthetics have been established that promote their safe use in dentistry (47). When used within acceptable dosage guidelines, these drugs are remarkably safe and few significant adverse drug reactions or drug interactions have been reported. Table 9 summarizes these adverse interactions.

Local anesthetics are all central nervous system depressants and function by inhibiting neuronal functions (253). Systemic adverse drug reactions associated with these agents are most often the result of excessive dosing resulting in central nervous

system depression manifested by lethargy, loss of consciousness and/or respiratory depression. For local anesthetics, selective depression of specific inhibitory neuronal pathways in the central nervous system may initially result in a preponderance of stimulatory activity, characterized clinically as tremors and convulsions (93, 162). Drug interactions that augment the severity of central nervous system depression are potentially life-threatening and therefore the greatest concern to general practitioners and specialists.

Summation reactions with local anesthetics

As described in the introduction, drugs with identical mechanisms of action and similar receptor sites will usually have additive effects when administered in combination, with the total pharmacological response of the combination being the summation of the individual drug actions. This generalization is certainly true for local anesthetic toxicity (57, 147). Administering 50% of the median toxic dose of a combination of two local anesthetics is equivalent to administering 100% of either anesthetic alone.

When considering anesthesia for adult dental patients, maximum safe dosage recommendations for local anesthesia permit volumes of solutions that are usually adequate for dental procedures. For adults, the maximum number of 1.8-ml cartridges of 2% lidocaine with 1:100,000 epinephrine is approximately 14, and for 3% mepivacaine the maximum number of cartridges is approximately seven (47). A summation drug interaction predicts that the maximum dose of a combination of these agents would be seen with seven cartridges of 2% lidocaine with epinephrine and 3.5 cartridges of mepivacaine. Summation drug interactions and local anesthetic toxicity become a concern when young children are being treated, when additional anesthetic is required for completing prolonged dental procedures, when excessive topical anesthesia is necessary to supplement regional anesthesia, or when a long-acting local anesthetic is administered for postoperative pain management. Maximum recommended dose calculations must consider the total dose of the combination of agents. Doses greater than the calculated maximum for a combination may be considered if sufficient time has elapsed to allow elimination of the initial doses, as might be seen when using an agent with a short metabolic half-life such as articaine (104). However, data supporting this assumption are currently limited. Combined use of local anesthetics at total doses that significantly exceed guidelines can cause classic local anesthetic toxicity reactions: central nervous system excitation, convulsions,

Table 9. Adverse drug interactions with local anesthetics

A. Summation interactions
Example: lidocaine with bupivacaine
Local anesthetic toxicity is additive when given in combination; although combination therapy with local anesthetics is acceptable, total dose should not exceed the calculated combined maximum recommended doses
B. Amide local anesthetics with inhibitors of metabolism
Example: lidocaine with cimetidine; or lidocaine with propranolol
This interaction is reported when lidocaine is administered as an infusion for cardiac arrhythmias. Inhibition of local anesthetic metabolism will have little effect on peak plasma levels or toxicity when given during a single appointment for dental anesthesia
C. Local anesthetics with opioid sedation
Example: mepivacaine with meperidine
Sedation with opioids may increase the risk of local anesthetic toxicity particularly with children. It is recommended that one reduce the local anesthetic dose when using opioid pharmacosedation
D. Ester local anesthetics with sulfonamide antibiotics
Example: procaine with sulfamethoxazole
Although procaine and other ester local anesthetics are infrequently used, the common metabolite *p*-amino benzoic acid may transiently reduce sulfonamide antibiotic efficacy
E. Local anesthetics with strong oxidizing drugs
Example: prilocaine with dapsone
Methemoglobinemia is usually the result of prilocaine dosing in excess of its maximum safe dosage recommendations. Increased risk of methemoglobinemia may be possible when oxidizing drugs are administered concurrently

respiratory depression, and cardiac arrest (93, 162). Fortunately, most dental practitioners are aware of this interaction and prevent its occurrence by limiting the total dosage of local anesthetics administered.

Amide local anesthetics with inhibitors of metabolism

Following absorption from the intraoral injection site, amide local anesthetics such as lidocaine and mepivacaine are broken down primarily in the liver. The metabolic reactions usually involve dealkylation of the terminal nitrogen of the local anesthetic with subsequent oxidation, hydrolysis, and/or conjugation. Elimination half-lives for amide local anesthetics used in dentistry are relatively short and peak plasma concentrations are usually seen within 45 minutes of administration. For drugs such as dental anesthetics, which undergo hepatic metabolism and have short metabolic half-lives, hepatic blood flow is the rate-limiting variable in drug elimination.

Some concern exists that impaired hepatic function, as a result of chronic liver disease or concomitant drug therapy, may decrease the rate of local anesthetic elimination, resulting in an elevation of peak plasma concentrations. This concern is most significant with multiple dosing or steady-state infusion therapies, as when intravenous lidocaine is used to manage cardiac arrhythmias. The peak plasma drug concentration following a single administration of a local anesthetic is primarily determined by the rate of systemic absorption and tissue distribution. The role of hepatic function in elevating peak blood concentrations of a drug is most significant following prolonged multidose and steady-state therapies. Changes in hepatic metabolic function, and subsequently lidocaine's elimination half-life, will cause only a minimal elevation of the peak blood concentrations following single-dose anesthetic therapy.

Cimetidine (Tagamet®) is an H_2-histamine antagonist that is known to inhibit the hepatic oxidative enzymes needed for the metabolism of many drugs including lidocaine (Table 2). By slowing the elimination of lidocaine, blood concentrations following steady-state infusion may increase by as much as 50% (85). Lidocaine toxicity following the single administration of dental anesthesia as a result of co-administration of cimetidine is unlikely and unreported. The inhibition of metabolism seen with cimetidine is not seen with other H_2-histamine antagonists such as ranitidine (Zantac®) or famotidine (Pepcid®) (127, 203).

The β-adrenergic blocker propranolol (Inderal) can decrease hepatic blood flow by 11% and reduce the clearance of lidocaine by as much as 40% (25). As with the previously discussed drug interaction with cimetidine, lidocaine blood concentrations may remain elevated for an extended period. The beta-blockers atenolol and pindolol do not appear to significantly inhibit lidocaine's metabolism (163). This mechanism primarily involves the rate of drug elimination and not absorption so peak blood concentrations of lidocaine following a single dose for dental anesthesia therapy may increase only minimally when a patient is taking propranolol. Adverse reactions reported in the literature appear limited to intravenous lidocaine infusions for cardiac arrhythmias. As will be discussed below, a greater concern with propranolol is its interaction with the epinephrine that is included in most local anesthetic formulations.

Local anesthetics with opioid sedation

Because local anesthetics are membrane depressants, following their absorption into the systemic circulation, they can alter central nervous system and cardiovascular function. The systemic depressant effects of local anesthetics and the possible interactions with other central nervous system depressants are most evident when treating pediatric dental patients. Maximum recommended safe doses for local anesthetics are based on body weight: a 50-lb (23-kg) child should receive one-third the dose of a 150-lb (68-kg) adult. However, the lower body weight of a child does not represent a proportionate decrease in orofacial anatomy. Because the mandible and maxilla of a 50-lb child are not one-third the size of a 150-lb adult, there is an apparent need to use relatively larger volumes of local anesthetics than would be predicted by body weight. As a consequence, local anesthetic toxicity is more frequently reported in children, and systemic drug interactions involving local anesthetics and other central nervous system depressant drugs become a greater concern.

The use of opioids as part of a pediatric sedation regimen has been associated with reports of local anesthetic toxicity reactions (93, 167). The mechanism for this interaction is probably multifaceted. In part, synthetic opioids, such as meperidine, have convulsant properties when excessive doses are administered (17, 89, 221). The opioid component of the sedation may also induce a mild respiratory acidosis that would decrease protein binding of local anesthetics, thereby permitting more unbound drug

to distribute to the central nervous system (38). Finally, the elevation of arterial carbon dioxide tensions that occurs with opioid premedication is known to increase central nervous system sensitivity to local-anesthetic-induced convulsions (133).

Classic local anesthetic overdose reactions, including central nervous system excitation, convulsions, respiratory depression, and cardiac arrest, have been reported when large doses of local anesthetics and sedative doses of opioids are combined in pediatric sedation. Practitioners using sedative drug therapies for pediatric patients should have anesthesia training and be prepared to manage the serious reactions that are possible. This complication is best managed by prevention; doses of local anesthetic should be adjusted downward when sedating children with opioids.

Ester local anesthetics with sulfonamide antimicrobials

Sulfonamides act by competing with *p*-amino benzoic acid, a substrate required for bacterial synthesis of folic acid. Procaine and tetracaine, two local anesthetics containing ester linkages, are broken down by plasma esterases into *p*-amino benzoic acid. Metabolism of these ester local anesthetics may increase the concentration of *p*-amino benzoic acid available to bacteria, thereby antagonizing the sulfonamide inhibition of bacterial growth. This adverse drug interaction may theoretically cause a reduction in sulfonamide antibacterial activity following the use of procaine for dental anesthesia (249). However, this drug interaction is dose dependent, transient, and would at most have only a minor effect on the overall course of the sulfonamide antibiotic therapy. Also its significance in dentistry is questionable, particularly because injectable ester local anesthetics have little indication in modern dental anesthesia.

Prilocaine and benzocaine with oxidizing drugs

When administered in excessive doses, the dental anesthetics prilocaine and benzocaine (and rarely lidocaine and articaine) have been associated with the development of drug-induced methemoglobinemia. These agents, as well as nitroglycerin and various nitrite preparations, the antimicrobials dapsone and sulfonamides, and the analgesic phenacetin, can cause the oxidation of the iron atom within hemoglobin, producing methemoglobin (108). The risk factors for this reaction include extremes of age, anemia, respiratory disease, hereditary deficiencies in glucose-6-phosphate dehydrogenase, and methemoglobin reductase deficiencies as well as drug combinations of these oxidant drugs (146). The clinical sign of cyanosis is observed as blood concentrations of methemoglobin reach 10–20%, whereas dyspnea and tachycardia are observed as methemoglobinemia concentrations reach 35–40%. Almost all reports of methemoglobinemia with prilocaine and benzocaine are associated with excessive doses of these agents (108, 175). The 'reckless' administration of benzocaine as a spray to provide topical pharyngeal anesthesia for intubation, endoscopy, bronchoscopy, and transesophageal echocardiography procedures accounts for the vast majority of reported cases with this drug (108). Case reports of concomitant drug therapies (dapsone, sulfonamides, nitrates, etc.) increasing the risk of local-anesthetic-induced methemoglobinemia in the dental setting have not appeared in the literature. It is recommended that the dose of local anesthetic be calculated carefully and that the weight-based maximum safe dosage recommendations not be exceeded, especially with very young or very old patients having known risk factors for methemoglobinemia, including concomitant drug therapy.

Adverse drug interactions involving dental vasoconstrictors

Certainly of all the drugs used or prescribed in dentistry, potential adverse drug interactions with vasoconstrictors are of most concern to the typical practitioner. Considering the overall magnitude of their use, reports of serious drug interactions with these agents in the outpatient dental setting have been exceedingly rare. One reason for this is that currently, epinephrine is by far the most widely employed vasonstrictor. While epinephrine has α1-adrenergic effects on some vascular beds, most notably under the skin and mucous membranes, leading to vasoconstriction, it also has vasodilatory effects on other vascular beds that contain predominantly β2-adrenergic receptors, such as those in skeletal muscle resulting in vasodilatation (Fig. 2) (251). This opposing vasodilatory property of epinephrine limits the potential pressor effects of the drug compared to other agents like levonordefrin and norepinephrine which have less, and in the case of norepinephrine almost no, β2-adrenergic activity (34, 234, 252). Typically most systemic effects of epinephrine, whether they involve myocardial

stimulation as a result of β1-adrenergic receptor activation or changes in vascular tone, are short lived because of the drug's short half-life in the bloodstream (120). For example, the intraoral injection of seven cartridges (11.9 ml) of articaine with 1:100,000 epinephrine (0.119 mg epinephrine total) in young healthy volunteers produced only small but significant ($P < 0.05$) increases in heart rate (nine beats per minute) and systolic blood pressure (6 mmHg) that had completely dissipated within 13 minutes of the final injection (104). In addition, the β2-adrenergic effects of epinephrine were demonstrated in this study by small decreases in diastolic blood pressure and total peripheral resistance.

Another factor adding to the safety of epinephrine in dental practice is that for the vast majority of dental procedures, adequate pain control and/or hemostasis usually requires far less local anesthetic and vasoconstrictor than employed in the study described immediately above. In fact the few deaths attributed to vasoconstrictor use in the dental office have involved excessive doses of epinephrine, typically in subjects with significant cardiovascular disease. A case describing a fatality in a 58-year-old dental patient with symptomatic angina and two previous myocardial infarctions, after the injection of five cartridges of 2% lidocaine plus 1:50,000 epinephrine (0.18 mg epinephrine total), clearly supports this assumption (250). In contrast to this tragic outcome, geriatric patients with a mean age of 70 years on various cardiovascular medications and with electrocardiogram-confirmed cardiac arrhythmias experienced no adverse sequelae during minor oral surgical procedures when the mean dose of epinephrine was limited to only 0.04 mg (40). So in reality most adverse events reported with epinephrine administration probably involve excessive dosing and/or poor aspirating technique in cardiovascularly compromised individuals, not adverse drug interactions. Still, based on the pharmacology of some potential interacting drugs, several case reports, and some limited drug interaction studies, caution in the use of vasoconstrictors in certain patient populations has been recommended (192, 252).

Epinephrine and levonordefrin with non-selective β-adrenergic blocking agents

Beta-adrenergic blocking agents are commonly employed in the treatment of hypertension, angina, and cardiac arrhythmias. They are classified as either being non-selective, meaning they block both β1 receptors on the heart and β2 receptors on the vasculature equally as well; or cardioselective, that is they preferentially block β1 receptors. Table 10 classifies some of the more commonly prescribed beta-blockers into these categories. As discussed before, epinephrine when absorbed systemically is not a pure vasoconstrictor because it activates both α1 and β2 adrenergic receptors (Fig. 2). However, if a non-selective beta-blocker such as propranolol is on board and significant systemic absorption of epinephrine occurs, the β2 vasodilatory effects (and the β1 cardiac stimulatory effects) of epinephrine will be blocked, allowing the α1 vasoconstrictive effects to function unopposed. In essence, the actions of epinephrine throughout the body would now resemble those of an almost pure vasoconstrictor like norepinephrine. Mean increases in systolic and diastolic blood pressure of 15–33 mmHg and 14–21 mmHg respectively have been demonstrated in hypertensive patients on propranolol therapy during intravenous epinephrine infusions of 0.016–0.032 mg, which is equivalent to slightly less than one or two dental local anesthetic cartridges containing 1:100,000 epinephrine. In contrast, when these same hypertensive patients were pretreated with the cardioselective β-adrenergic blocking agent metoprolol, epinephrine infusions only caused a rise in systolic blood pressure of 5–11 mmHg with no change in diastolic blood pressure (from –1 to 2 mmHg) (115). Similarly, in healthy men aged 38–46 years who were pretreated with propranolol, intravenous epinephrine infusions of 0.015 mg produced pronounced hypertension with a reflex bradycardia (38% decrease in heart rate) (151). Other studies on normotensive individuals have also documented the ability of propranolol to eliminate the β2 vasodilatory effect of infused epinephrine. While observing a fall in diastolic blood pressure of about 20 mmHg and a fall in total peripheral resistance with epinephrine infusions alone, diastolic blood pressure rose by about 20 mmHg and total peripheral resistance also increased when subjects

Table 10. Classification of some β-adrenergic blocking agents with common trade names in parentheses

Non-selective	Cardioselective
Propranolol (Inderal®)	Atenolol (Tenormin®)
Nadolol (Corgard®)	Metoprolol (Lopressor®)
Timolol (Blocadren®)	Acebutolol (Sectral®)
Sotalol (Betapace®)	Betaxolol (Kerlone®)

were pretreated with propranolol. When the same subjects were pretreated with the cardioselective β-adrenergic blockers metoprolol or atenolol significant increases in blood pressure or peripheral vascular resistance did not occur (111, 200). The lack of significant blood pressure changes with cardioselective β-adrenergic blockers such as metoprolol or atenolol is explained by their inability to block the β2 vasodilatory properties of epinephrine.

In normal volunteers pretreated with a single oral dose of the non-selective beta-blocker pindolol, small but significant increases in blood pressure and peripheral vascular resistance with corresponding decreases in heart rate and stroke volume were observed after the administration of two intraoral injections of 2% lidocaine plus 1:80,000 epinephrine (0.045 mg epinephrine total). When these same subjects were not pretreated with pindolol, the administration of local anesthetic plus vasoconstrictor induced small decreases in systolic and diastolic blood pressure, and peripheral vascular resistance (224). Finally, several case reports in patients undergoing plastic surgery have demonstrated serious sequelae including hypertension, cardiac arrest, and stroke after facial injections of local anesthetic volumes equivalent to two cartridges of 2% lidocaine plus 1:50,000 epinephrine (0.072 mg epinephrine total) in patients on non-selective β-adrenergic blockers (42, 84). One case of hypertension in a 32-year-old female dental patient taking propranolol for hypertension has been reported after the administration of 1½ cartridges of 2% mepivacaine plus 1:20,000 levonordefrin (160). Systolic and diastolic blood pressures increased by 40 and 15 mmHg, respectively. Fortunately these increases in blood pressure were transient. When this same patient was treated with two cartridges of 3% mepivacaine plain on a subsequent appointment, no change in any cardiovascular parameter was observed.

The interaction between epinephrine and levonordefrin with non-selective β-adrenergic blocking agents is potentially serious and well supported by clinical trials and a handful of case reports. The severity of the interaction appears to be dose related; small epinephrine doses cause less of a pressor response than larger doses (115). In addition, inadvertent intravascular injections of vasoconstrictor are more likely to result in a more pronounced response. Subjects with significant cardiovascular disease may be especially vulnerable to the most serious sequelae resulting from the pressor reactions of the drug combination. It is recommended that individuals on non-selective β-adrenergic blocking agents receive an initial test dose of between one-half and one cartridge of local anesthetic and then be monitored for increases in blood pressure before additional local anesthetic is administered (174). No more than 0.04 mg epinephrine or 0.2 mg levonordefrin (two cartridges of a 1:100,000 epinephrine solution or two cartridges of a 1:20,000 levonordefrin solution) should be administered in a single visit. Obviously if the procedure is short and hemostasis is not required, the complete avoidance of epinephrine or levonordefrin in these patients would also appear prudent. In addition, epinephrine-impregnated cord, which can contain as much as 0.5 mg racemic epinephrine per inch (0.2 mg/cm) (126), should be completely avoided in this patient population and in all patients on drugs with the potential to interact with dental vasoconstrictors.

Epinephrine and levonordefrin with tricyclic antidepressants

Antidepressant agents are divided into three different pharmacological groups; the selective serotonin reuptake inhibitors, the monoamine oxidase inhibitors, and the tricyclic antidepressants. Table 7 provides examples of agents from each classification. As shown in Fig. 2, while monoamine oxidase plays an important role in the degradation of endogenous norepinephrine, the effects of epinephrine, and in fact of other catecholamines administered via a dental injection, are primarily terminated by the enzyme catechol-*O*-methyltransferase and the adrenergic neuronal reuptake process (252). Widely promulgated cardiovascular interactions between monoamine oxidase inhibitors and dental vasoconstrictors therefore do not occur, and this has been supported by clinical experience and by human and animal studies (35, 174, 254). Likewise, because selective serotonin reuptake inhibitors block the serotonin reuptake pump and not the noradrenergic reuptake pump, they have also not been associated with adverse drug interactions with dental vasoconstrictors (28).

In contrast to monoamine oxidase inhibitors and selective serotonin reuptake inhibitors, based on the ability of tricyclic antidepressants to block the noradrenergic reuptake pump (Fig. 2), and because epinephrine and levonordefrin depend partly on this reuptake for removal from the synapse, the accumulation of epinephrine and levonordefrin in the vicinity of postsynaptic α- and β-adrenergic receptors could result, leading to enhanced cardiovascular activity. Pretreatment with the tricyclic antidepressant protriptyline three times per day for 4 days in

human volunteers induced significant increases in both systolic and diastolic blood pressure with epinephrine infusion rates of 0.067 μg/kg/min. One-third as much norepinephrine was required to produce the same effect (226). Similar results were reported in man by Boakes et al., while studies in dogs revealed that bolus injections of norepinephrine or levonordefrin in amounts resembling a one-cartridge intravascular injection in man produced a tripling and a doubling of mean arterial pressure, respectively, in animals pretreated with the tricyclic antidepressant desipramine compared to the injection of either vasoconstrictor alone (35, 254). Dysrhythmias were also reported with the norepinephrine or levonordefrin injections in desipramine-pretreated animals. In contrast, dogs pretreated with desipramine receiving an intravenous bolus of one cartridge of a 1:100,000 epinephrine solution, exhibited a fall in mean arterial pressure that was double that of epinephrine alone. Only when doses of epinephrine approached the equivalent of seven cartridges was a significant pressure response recorded (254).

While it has been argued and supported by laboratory studies that with chronic administration of tricyclic antidepressants, desensitization in the response to adrenergic vasoconstrictors may occur as a result of a downregulation of postsynaptic receptors (37, 245), vasoconstrictors should still be used cautiously in these patients until further clinical research indicates differently. Levonordefrin and norepinephrine should be avoided and epinephrine dosages should not exceed 0.054 mg or the amount in three cartridges of a 1:100,000 solution. Felypressin, where available as a vasoconstrictor, appears to be a safe alternative in this patient population (3, 91, 191).

Epinephrine and levonordefrin with cocaine

While remaining a useful drug because of its profound topical anesthetic and hemostatic effects during nasal surgery, illicit consumption via snorting, injection, and smoking unfortunately accounts for the greatest use of cocaine (137, 188). Cocaine possesses tricyclic antidepressant-like activity and may also enhance adrenergic neurotransmitter release and postsynaptic responses to epinephrine-like drugs (252). A number of deaths have been attributed to acute cocaine use and the ability of the drug to induce myocardial stimulation and dysrhythmias while at the same time constricting the coronary arteries is thought to contribute to these fatal outcomes (137, 188). In addition, seizure activity produced by the central nervous system excitatory action of the drug further enhances the pressure effect of cocaine and can lead to cerebral vascular accidents (137). Chronic cocaine abusers may also develop underlying cardiovascular disease including cardiomyopathies (137), making them more susceptible to significant morbidity following cardiovascular stimulation.

With respect to dental vasoconstrictors, there is one well-documented case of a myocardial infarction in an otherwise healthy young man who received an injection of lidocaine with epinephrine after the application of topical cocaine for nasal surgery (44). Other reports of deaths in medicine and dentistry are alleged to have occurred from this combination (252). It is thus not surprising that concern exists regarding the administration of dental vasoconstrictors in this patient population (192, 252). Patients who have recently self-administered cocaine are poor candidates for dental care regardless of vasoconstrictor administration, because of the agitation, hypertension, and cardiac arrhythmias associated with the illicit use of the drug. Dental care including the use of vasoconstrictors should be withheld until at least 48 hours after the last dose of cocaine (174). In patients with cocaine-related cardiomyopathies or patients where the veracity of a lack of recent cocaine use is in doubt, treatment should preferably take place in a hospital setting (188).

Epinephrine and levonordefrin with attention deficit hyperactivity disorder drugs

Attention deficit hyperactivity disorder is the most common neurobehavioral disorder affecting school-aged children with an overall incidence approaching 10% of the population. Often the symptoms persist into adolescence and adulthood, causing significant lifelong impairments in academic, career, and social functioning (149). Common drugs employed for the disorder include the norepinephrine reuptake inhibitor atomoxetine (Strattera®) and amphetamine or amphetamine-like stimulants (Table 11) (168). While not classified as a stimulant, the actions of atomoxetene resemble those of tricyclic antidepressants, thus the same dosage limitations on epinephrine and avoidance of levonordefrin are advised. Stimulant attention deficit hyperactivity disorder drugs both increase the release of norepinephrine and other catecholamines and also block their reuptake (149, 180). Based on the recent recommendations of the Drug Safety and Risk Management Advisory

Table 11. Commonly prescribed attention deficit hyperactivity disorder drugs with trade names in parentheses

Methylphenidate (Ritalin®, Concerta®, Metadate®, Methylin®)
Dexmethylphenidate (Focalin®)
Dextroamphetamine (Dexedrine®)
Amphetamine salt mixtures (Adderall®)
Pemoline (Cylert®)
Atomoxetine (Strattera®)

Committee and the Pediatric Advisory Committee to the Food and Drug Administration (177, 180), the Food and Drug Administration has issued additional warnings concerning increased risks of cardiovascular events including myocardial infarction and stroke in both children with pre-existing cardiovascular disease and adult users of attention deficit hyperactivity disorder stimulant drugs, including caution in the use of other vasopressor drugs (2). While definitive adverse reactions between attention deficit hyperactivity disorder stimulant drugs and dental vasoconstrictors have not been reported, monitoring of blood pressure and heart rate in these patients is advised. In children and adults with normal blood pressures and heart rates, small amounts of epinephrine (0.04–0.054 mg) or levonordefrin (0.2 mg) can be employed with careful aspirating technique. Patients who present to the dental office with significantly elevated blood pressure or significant tachycardia should not receive elective care that day and should be referred back to their treating physician.

Epinephrine and levonordefrin with catechol-*O*-methyltransferase inhibitors

Tolcapone (Tasmar®) and entacapone (Comtan®) are recently introduced drugs in the management of Parkinson's disease as adjuncts to levodopa/carbidopa (Sinemet®) therapy. By reversibly blocking catechol-*O*-methyltransferase, they inhibit levodopa inactivation in the periphery (204). As shown in Fig. 2, these drugs could also inhibit the inactivation of exogenously administered epinephrine and levonordefrin contained in a local anesthetic solution because they are also substrates for catechol-*O*-methyltransferase. In healthy volunteers, a single dose of entacapone was reported to increase the tachycardia experienced after an epinephrine infusion by 80% compared to a placebo control, with one healthy subject experiencing a significant ventricular tachycardia that necessitated propranolol reversal (119). While no cases of adverse interactions have appeared in the dental setting, these drugs are relatively new, so caution in vasoconstrictor dosing is advised. It has been recommended that no more than the equivalent of one cartridge of lidocaine with 1:100,000 epinephrine be administered initially and to monitor the patient's blood pressure and heart rate before administering any additional local anesthetic with vasoconstrictor (204).

Epinephrine and levonordefrin with adrenergic neuronal-blocking agents

Guanethidine (Ismelin®) and guanadrel (Hylorel®) both deplete and inhibit the release of norepinephrine from adrenergic nerve terminals (252). Their use in treating hypertension has diminished because of an unfavorable side effect profile. Their long-term use has been reported to cause an upregulation of postsynaptic α and β receptors and an inhibition of catecholamine reuptake, thus the possibility exists that if sufficient epinephrine or levonordefrin is injected or absorbed into the bloodstream, exaggerated cardiovascular responses could occur. Significantly increased pressor responses with more frequent cardiac arrhythmias have occurred in subjects pretreated with guanethidine who received norepinephrine infusions than with norepinephrine infusions alone (172). In the few patients who still may be taking adrenergic neuronal blocking agents the epinephrine dose should not exceed 0.054 mg and careful aspirating technique is advised. Since the effect seems more pronounced with purer α-adrenergic stimulants (221), levonordefrin and norepinephrine should be avoided.

Epinephrine and levonordefrin with digitalis glycosides

The two most commonly employed digitalis glycosides in the treatment of congestive heart failure are digoxin (Lanoxin®) and digitoxin (Crystodigin®). Both are positive inotropes with low therapeutic indices with their most critical side effect being ventricular arrhythmias. In addition, these patients are 'more fragile', because of their disease condition, than healthy young adults in the dental chair. A leading drug interaction text lists 275 potentially interacting drugs (not all well documented) for digoxin alone, and somewhat surprisingly epinephrine or levonordefrin are not listed among them (221). Still the cautious use of dental vasoconstrictors is advised in

this population because excessive administration of epinephrine or levonordefrin to subjects on digitalis glycosides at the very least could induce additive dysrhythmogenic activity. Careful aspirating technique and limiting the epinephrine or levonordefrin dose to no more than 0.04 or 0.20 mg, respectively, is advised.

Conclusions

Dental clinicians need to remain vigilant in recognizing and preferably preventing adverse drug interactions in their patients. With the continued introduction of new therapeutic classes of drugs, the number of potential adverse drug interactions will continue to grow. An up-to-date medical history with careful querying of patient medication intake is the logical place to start in any attempt to prevent adverse drug interactions. It is incumbent upon the practitioner to try to stay abreast of this ever-evolving field, especially as it relates to dental therapeutics.

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