Literature Review

Old Drugs, New Uses

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Abstract: *Advances in pediatric health care have prolonged lives and improved the quality of life for children and adolescents. These advances include not only high-tech devices and new medications but also re-application of available medications to take advantage of unexpected benefits which may not have been known previously or even side effects that can have therapeutic value for diseases and conditions refractory to other treatment. This review describes new uses for anti-epileptic medications, thalidomide, intravenous immunoglobulin, hydroxyurea, methotrexate, botulinum toxin, bisphosphonates, and aspirin in the medical care of children. Methods of action and concerns for the pediatric dentist are described for children benefiting from these new applications. (Pediatr Dent 2011;33:67-74) Received August 19, 2009 / Last Revision November 14, 2009 / Accepted November 14, 2009*

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Understanding a patient's medical history is of paramount importance in the practice of dentistry. Advances in therapy have led more children and adolescents with chronic diseases and conditions to enjoy longer and healthier lives, so the pediatric dentist often must become familiar with an entire new regimen of drugs and medical devices that physicians use to cure disease, prolong life, and improve the quality of life.

Medications used solely for adults in the past are now being prescribed for young patients because of their clinical benefits, often without official approval ("off-label use"); in fact, as much as 50% of pediatric use of medications is considered off-label. Furthermore, clinicians and researchers have learned that many drugs originally administered for one purpose can cause an unexpected positive effect that can be used to manage or cure resistant conditions (Table 1). A common example discussed later in this paper is the use of aspirin, a potent anti-inflammatory and antipyretic for its anticoagulant properties in heart disease. Observations of the side effects of longstanding drugs have led to new uses, and numerous clinical trials are currently being conducted to understand new uses for old drugs.

The result of this new pharmacology is that the pediatric dentist cannot assume that the indication-treatment paradigm is what he or she learned in school. Furthermore, as is often the case with the reintroduction of longstanding medications for new purposes, the mechanism of action may be unknown, even for prescribers, or may be counterintuitive. Furthermore, the paradigm is complicated not just from new uses for existing drugs, but from the cascade of consequences of survivorship. Physicians choose drugs to manage these medication side effects, often introducing even more complications. Surviving children also may suffer organ damage and altered physiology, requiring still another set of drugs.

The rapidity of change in pediatric health care makes it difficult for the clinician to keep abreast of new therapies. Hence, the purpose of this paper was to present a brief overview of several medications and products used in pediatrics for which new applications have emerged in the past few years. Pediatric dentists must be alert to the fact that many of them may require modifications for safe delivery of care while others may cause adverse effects in the oral cavity.

Antiepileptic drugs and devices. Besides treating seizure disorders, antiepileptic drugs (**AEDs**) and devices (Table 2) have been used to manage other neurological conditions, psychiatric disorders, and pain syndromes. In neurology, they are useful in the treatment of neuropathic pain, migraines, and essential tremors, a progressive neurological disorder.[1] AEDs may be able to dampen many proposed causes of chronic pain, such as peripheral and central sensitization, hyperexcitability, and neuronal disinhibition.[2] Pregabalin is approved by the Food and Drug Administration (**FDA**) for the treatment of neuropathic pain associated with diabetic polyneuropathy and postherpetic neuralgia for which gabapentin also is indicated.[1,2] The latter can be also used for the management of diabetic neuropathy, migraine, spinal cord injury, and phantom limb.[2] Migraine, which is a common comorbidity of epilepsy, can be prevented with broad spectrum drugs such as valproate and topiramate.[1,2] Carbamazepine is the first-line therapy for the management of idiopathic trigeminal neuralgia.[2] Lamotrigine also is useful in cases of central poststroke pain, painful

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human immunodeficiency virus (HIV) neuropathy, trigeminal neuralgia, and spinal cord injury.[2]

The incidence of psychiatric disorders is significantly higher in epileptic patients than in the general population, with anxiety and bipolar disorder being common comorbidities. Although carbamazepine, valproate, and lamotrigine are the only FDA-approved AEDs for the treatment of a psychiatric disorder, virtually every other new AED claims efficacy for some psychiatric symptoms or disorders such as anxiety, schizophrenia, social phobia, post-traumatic stress disorder, and mood disorders[1,2]—conditions which are increasingly more common in children.[3] An interesting recent finding regarding the vagus nerve stimulator, an implantable pulse generator that is used to reduce the frequency and severity of seizures, is its antidepressant effects, which may be more sustained than typical therapies. Thus, the device has received FDA approval for use in treatment-resistant depression.[2]

Growing evidence supports AEDs as useful in the treatment of some eating disorders, given that many of the drugs have effects on the neural systems involved in the regulation of feeding behavior and weight control, a growing concern in children. Valproate, gabapentin, and pregabalin are associated with weight gain and increased appetite, whereas topiramate, zonisamide, and felbamate are linked to weight loss and decreased appetite.[4] Many eating disorders are associated with conditions for which AEDs have efficacy. Carbamazepine and valproate may be effective in the treatment of patients with bulimia or anorexia nervosa when they are used to treat an associated psychiatric or neurological disorder.[4]

Topiramate is useful as an antibinge eating, antipurging and weight loss agent in bulimia nervosa and binge-eating disorder with obesity.[4] It also may have beneficial effects for night-eating syndrome and sleep-related eating disorder sufferers. Phenytoin may be effective in the management of compulsive binge eating and/or anorexia nervosa patients who also present electroencephalogram abnormalities or epilepsy,[4] placing them at risk for gingival overgrowth. Oxcarbazepine has been successful in the control of self-mutilating behaviors in eating disorder patients.[5]

Pediatric dentists should be aware of new areas of action for AEDs, including: tardive dyskinesia; substance use disorder; spasticity; myotonia; neonatal cerebral hemorrhage; and neurodegenerative conditions, such as HIV-associated dementia, Alzheimer's disease, and Parkinson's disease.[1] Valproic acid is currently being studied for use in leukemias and solid tumors, given its ability to interfere with multiple processes in cancerous cells.[6] AEDs may cause adverse effects of concern for the pediatric dentist, such as: blood dyscrasias; increased oral secretions or dry mouth; behavioral change; liver dysfunction; and gingival overgrowth. Unanticipated benefits in breakthrough care from clinical trials of AEDs for nonepileptic conditions in children and adolescents, however, also will become more frequent in the near future.

Thalidomide. Thalidomide was synthesized in 1954 as an anticonvulsant agent but was found to be an effective sedative and sleep-inducing agent in humans as well as an effective antiemetic in pregnancy. Reports of teratogenic effects, such as phocomelia, started appearing in 1956—leading to its market withdrawal in 1961.[7] The drug was never approved for use in the United States because an FDA

Table 1. ORIGINAL AND SELECTED NEW INDICATIONS FOR SOME ESTABLISHED DRUGS

Drug class	Original indication(s)	New indication(s)
Acetylsalicylic	Analgesic	Antiplatelet therapy
Antiepileptic drugs	Epilepsy	Neurological conditions, psychiatric disorders, pain syndromes, eating disorders
Bisphosphonates	Postmenopausal and steroid-induced osteoporoses	Primary and secondary osteoporoses, hypercalcemia of malignancy, metastatic bone disease in cancer, multiple myeloma
Botulinum toxin	Strabismus, blepharospasm	Hyperhydrosis, cervical dystonias, facial frown lines, spasticity, hyperlacrimation, bruxism, rhinitis, hemifacial spasm, Tourette's syndrome, incontinence, salivary secretory disorder, trismus myofacial pain, headache
Hydroxyurea	Psoriasis, polycythemia vera, cancer, thrombocythemia	Sickle cell disease
Intravenous immunoglobulins	Infectious diseases, congenital immunodeficiencies, hypogammoglobulinemia	Pediatric HIV infections, ITP, Kawasaki disease, CLL, prevention of GVHD and infections in HSCT, Guillain-Barre syndrome, autoimmune diseases
Methotrexate	Cancer	Juvenile idiopathic arthritis, psoriasis, inflammatory bowel disease, prevention of GVHD in HSCT
Thalidomide	Epilepsy, sedation, antiemetic in pregnancy	Leprosy, multiple myeloma, myelodysplastic syndrome, Behcet's disease, SLE, aphthous ulcers, erythema multiforme, Crohn's disease, treatment of post-HSCT GVHD

* SLE=systemic lupus erythematosus; HSCT=hematopoietic stem cell transplantation; GVHD=graft-vs-host disease; HIV=human immunodeficiency virus; ITP=idiopathic thrombocytopenic purpura; CLL=chronic lymphocytic leukemia.

Table 2. COMMONLY USED FIRST AND SECOND GENERATION ANTIEPILEPTIC DRUGS

First generation	Second generation
Generic name (brand name)	Generic name (brand name)
Carbamazepine (Tegretol)	Felbamate (Felbatol)
Clonazepam (Klonopin)	Fosphenytoin (Cerebyx)
Ethosuximide (Zarontin)	Gabapentin (Neurontin)
Phenobarbitol (Luminal)	Lamotrigine (Lamictal)
Phenytoin (Dilantin)	Levetiracetam (Keppra)
Primidone (Mysoline)	Oxcarbazepine (Trileptal)
Valproate (Depakote, Depakene)	Pregabalin (Lyrica)
	Topiramate (Topamax)
	Tiagabine (Gabitril)
	Vigabatrin (Sabril)
	Zonisamide (Zonegran)

reviewer demanded more information from the manufacturer about reports of peripheral neuritis, but the company never responded and eventually withdrew its application.[7,8]

Thalidomide and its immunomodulatory analogues (IMiDs) affect the body's immune system in many ways, including potential anti-inflammatory and anticancer properties.[7] Thalidomide was FDA-approved for a painful inflammatory dermatological manifestation of leprosy called erythema nodosum leprosum in 1998.[7,8] Both thalidomide and its analogue lenalidomide have received FDA approval for the treatment of multiple myeloma and myelodysplastic syndrome.[8] The efficacy of thalidomide has been verified in a number of conditions affecting the skin and mucosa, including: Behçet's disease; graft-vs-host disease (GVHD); aphthous ulcers; actinic prurigo; erythema multiforme; refractory Crohn's disease; complex regional pain syndrome; discoid lupus; and the skin manifestations of systemic lupus erythematosus.[7,9]

Because aphthous ulcers tend to resolve on their own and because of the potentially serious adverse effects of thalidomide, therapy should only be initiated in cases of severe, recurrent, or refractory ulcers.[9] The drug is a useful option, however, for children with Behçet's disease whose severe oral and genital lesions are unresponsive to other treatment.[10] The drug is currently being used experimentally to treat dermatological, neurological, and inflammatory diseases, as well as many types of cancers, including: glioma; metastatic melanoma; hematologic malignancies; and cancer of the pancreas, breast, and lung.[7,8] Second generation IMiDs such as lenalidomide (CC-5013) and CC-4047 are 2,000 and 20,000 times more potent, respectively, than thalidomide but lack its significant neurosedative toxicity.[7-9] Dose-limiting neutropenia and thrombocytopenia are the most common problems with the IMiDs, while venous thromboembolism occurs with all 3 agents.[8] Neutropenia is a very rare side effect of thalidomide, occurring in fewer than 1% of patients.[9]

Intravenous immunoglobulin. Another drug increasingly used for treatment of refractory conditions is intravenous immunoglobulin (IVIG). It is a product that is physiologically and pharmacologically the same as immunoglobulin taken from the human body, because it is purified from pooled human plasma from healthy donors, leading to a relatively pure concentrate of IgG, with traces of other immunoglobulins.[11-14] Due to the wide variety of immunoglobulins in the preparation, it was originally used to treat infectious diseases, congenital immunodeficiency, and hypogammoglobulinemia.[12,14] IVIG also is known to increase the platelet count, which is why it is so effective in idiopathic thrombocytopenic purpura (ITP), a disease of children.[13]

To guarantee the required level of quality and safety, manufacturers carefully select plasma donors, screen plasma samples for transmittable infectious agents, and use modern viral inactivation techniques.[11] These safety parameters have led to a low incidence of side effects and to the product's increased clinical use. The FDA-approved indications for its use, however, are few: (1) pediatric HIV infections; (2) ITP; (3) Kawasaki disease; (4) primary immunodeficiency/ hypogammoglobulinemia; (5) secondary immunodeficiency in chronic lymphocytic leukemia; and (6) prevention of infections and GVHD in hematopoietic stem cell transplantation (HSCT).[12-14] More than half of clinical IVIG use, however, is for "off-label" indications (Table 3).

The FDA does not restrict or interfere with the clinical practice of approved products. Thus, in practice, clinicians can use IVIG for any indication for which they perceive a patient benefit. Hence, its use is growing.[15] Although not officially approved by the FDA, IVIG is accepted as the first line of treatment in Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, dermatomyositis, stiff-person syndrome, multifocal motor neuropathy, and various autoimmune diseases, among other conditions.[12,15]

IVIG is dosed according to the underlying medical condition, and no drug interactions have been reported.[11] Approximately 10% of patients present side effects, which are usually transient and self-limited and occur primarily within the first few hours of infusion up to 3 days later.[11,14] They most commonly include headache, low grade fever, muscle, back and joint pain, nausea, vomiting, and abdominal pain. Severe complications, such as acute renal failure, stroke, deep venous thrombosis, myocardial infarction, and anaphylactic reaction, are rare.[11] Unfortunately, IVIG products are very expensive, averaging $50 to $80 (US) per gram for a standard adult course and costing approximately $2,700 (US)

Table 3. OFF-LABEL USES OF INTRAVENOUS IMMUNOGLOBULIN[10,13,14]

Cardiovascular conditions	Atherosclerosis, rejection in cardiac transplantation, myocarditis, congestive heart failure, dilated cardiomyopathy, pericardial diseases
Dermatological conditions	Atopic dermatitis, chronic urticaria, epidermolysis bullosa acquisita, pemphigus vulgaris, mucous membrane pemphigoid
Infections	Chronic parvovirus B19 infection toxic shock syndrome or toxic necrotizing fasciitis due to group A streptococcus
Neuroimmune disorders	Gullain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, dermatomyositis, multifocal motor neuropathy
Rheumatology	Systemic lupus erythematosus, vaculitis
Secondary immunodeficiency	Multiple myeoloma, organ transplantation, hematological malignancies, extensive burns, and collagen-vascular diseases

Table 4. COMMERCIALLY AVAILABLE BOTULINUM TOXINS

Type A drug (generic name, brand name and manufacturer)	Type B drug (generic name, brand name and manufacturer)
OnabotulinumtoxinA	*RimabotulinumtoxinB*
Botox and Botox Cosmetic, (Vistabel (Allergan Ltd, Bucks, Calif)	Myobloc and NeuroBloc (Solstice Neuroscience Inc, South San Francisco, Calif)
AbobotulinumtoxinA	
Dysport (Ipsen Group, Brisbane, Calif)	
IncobotulinumtoxinA	
Xeomin (Merz Pharmaceuticals, Frankfurt, Germany)	

per infusion.[11,13,15] Therefore, the cost-benefit ratio must be considered carefully before prescribing it. An example is bacterial infection prophylaxis in which IVIG has not shown a decrease in mortality and incidence of serious infections compared to the much cheaper antibiotic alternative.[13]

Hydroxyurea. Clinicians who treat children with sickle cell disease (**SCD**) will begin to see the use of hydroxyurea (**HU**) increase. HU was synthesized in Germany in 1869 and has been used to treat psoriasis, polycythemia vera, essential thrombocythemia, myeloproliferative syndromes, some types of leukemia, melanoma, and ovarian cancer.[16,17] The drug was first studied in SCD in 1984 and was FDA-approved in 1998 for use in adults only.[18]

In SCD, erythrocytes become deoxygenated, dehydrated, and crescent-shaped ("sickled") under certain circumstances, aggregating and sticking to blood vessel walls—which leads to blockage of blood flow to limbs and organs. In turn, this causes severe painful episodes and permanent damage to the eyes, brain, heart, lungs, kidneys, bones, and spleen.[16] HU is efficacious in the treatment of SCD because it increases the production of fetal hemoglobin-containing erythrocytes, which are less likely to sickle. It also dilutes the number of sickled cells in circulation and may reduce cell adhesion that contributes to vaso-occlusion, thus decreasing severe painful episodes, hospitalizations, blood transfusions, and acute chest syndrome.[16,18]

The evidence of its efficacy in adults is very strong, but that is not yet the case in children. Emerging data are encouraging, however, and clinical experience shows that it is highly effective in widespread practice.[16,18] The spleen, a very important organ that is often affected in SCD, also can recover its functions after treatment with HU, saving the young patient from the risks of abdominal surgery and sepsis.[19] Unfortunately, there is a problem with patient compliance, given that it takes between 3 to 6 months of drug use to see a clinical response.[16]

There are side effects of HU that pediatric dentists should be aware of when treating SCD children. As a chemotherapeutic drug, HU affects rapidly dividing cells, particularly newly formed blood cells. The short-term effects are dose-related and include leukopenia, thrombocytopenia, anemia, and oral mucositis, all usually resolving within 1 to 2 weeks.[16,19] The drug also may decrease sperm production in men. Its potential long-term effects, although not yet proven, may include teratogenic defects, growth delays in children, and cancer in both children and adults, leading to the underutilization of the drug.[16] The number of birth defects in offspring of women who took HU during pregnancy, however, does not seem to be increased.

Children who have SCD and take the drug have shown similar growth rates to their peers who did not receive it. Furthermore, the risk for cancer does not seem higher for SCD patients who have taken HU vs those who have not.[16] Cutaneous and oral squamous cell carcinomas and basal cell carcinomas have been reported following administration of HU.[17] Given that patients may be immunosuppressed after using HU, the pediatric dentist must consult with the hematologist and understand the patient's blood counts before providing dental care.[20]

Methotrexate. Methotrexate (**MTX**) is a folic acid analog that inhibits dihydrofolate reductase, an enzyme needed for DNA synthesis, repair, and cellular replication.[21,22] Actively proliferating tissues, such as the oral mucosa, bone marrow, and malignant cells, are very sensitive to MTX. Therefore, it has been FDA-approved for treatment of non-Hodgkin's lymphomas, acute lymphocytic leukemia, and cancer of the uterus, breast, lungs, and head and neck.[23]

Pediatric dentists may not be aware that MTX has been increasingly used in low-dose regimens for a variety of noncancerous conditions. The main indication for low-dose MTX is weekly administration in children and adolescents diagnosed with juvenile idiopathic arthritis (**JIA**).[22,24] The drug is started if therapy with an adequate dose of a nonsteroidal anti-inflammatory drug over 6 to 8 weeks and/or local therapy with corticosteroids has not led to clinical remission.[22] MTX also is used for treatment of psoriasis, but does not clear psoriatic skin lesions permanently in most patients. Hence, they need maintenance therapy for long-term disease control.[21] Other indications for low-dose MTX include: inflammatory bowel disease; musculoskeletal manifestations of sarcoidosis; prophylaxis against GVHD following HSCT; and systemic lupus erythematosus (SLE), among others.[24] Safety and effectiveness of the drug in pediatric patients have been established only in cancer chemotherapy and JIA.[23]

Pregnancy is an absolute contraindication for the use of MTX because it can cause fetal death and possibly teratogenic defects.[21-23] Adverse reactions

Table 5. COMMERCIALLY AVAILABLE BISPHOSPHONATES

Generic name	Brand name (manufacturer)	Route	Potency
First generation			
Etidronate	Didronel (Procter and Gamble, Cincinnati, Ohio)	Oral/IV	1
Clodronate	Bonefos (Bayer HealthCare Pharmaceuticals, Montville, NJ)	Oral/IV	10
Tiludronate	Skelid (Sanofi-Aventis, Bridgewater, NJ)	Oral	10
Second generation			
Pamidronate	Aredia (Novartis, East Hanover, NJ)	IV	100
Alendronate	Fosamax (Merck, Whitehouse Station, NJ)	Oral	1,000-10,000
Third generation			
Ibandronate	Boniva (Roche/Genentech, South San Francisco, Calif)	Oral/IV	1,000-10,000
Risedronate	Actonel (Warner Chilcott Pharmaceuticals, Mason, Ohio)	Oral/IV	1,000-10,000
Zoledronic acid	Reclast and Zometa (Novartis, Stein, Switzerland)	IV	>10,000

may occur, especially when used in high doses. In low doses, however, they may be minor and resolve spontaneously.[22,24] Side effects include mucositis, taste disturbance, nausea, anorexia, headaches, fever, chills, fatigue, pruritus, skin pain, urticaria, alopecia, acute depression, teratogenesis, and nephropathy, among others.[21,22,24] The pediatric dentist should be aware that the drug may induce or exacerbate a wide variety of oral lesions, ranging from nonhealing ulcers to destructive lymphoma-like lesions.[24] It may be necessary to replace it early with another agent in patients with persistent mucositis that does not respond to treatment.[24]

Hematotoxicity is rare and consists of leukocytopenia, anemia, and/or thrombocytopenia.[22,23] A relationship between MTX and lymphoproliferative disorders has been suggested, but most consider it to just be coincidental.[21,24] Opportunistic infections during MTX administration can be seen, particularly in the presence of leukopenia and even in low doses.[21,22] The drug may lead to osteopathy in children due to an adverse effect on bone metabolism, especially on osteoblast activity.[21] Some authors suggest discontinuing MTX for a few days before and after significant surgical procedures because it may increase postoperative infections and delay wound healing.[21]

Some medications used in dentistry, such as nystatin, polymixin B, vancomycin, barbiturates, tranquilizers, nonsteroidal inflammatory drugs, salycilates, and penicillins, may reduce MTX absorption.[21,23] MTX given together with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.[23] The pediatric dentist should consult with the physician regarding drug interactions as well as the patient's immune status before proceeding with invasive dental care.

Botulinum toxin. Botulism is food poisoning caused by *Clostridium botulinum*, a gram-positive anaerobe that is found ubiquitously in soil and water.[25,26] The first case was documented following consumption of meat and blood sausages in 18th century Germany, but the causative pathogen was only discovered in Belgium in 1895.[26] The term "botulism" comes from the Latin "botulus" which means sausage and not from the sausage-like shape of C. botulinum.[26] Modern use of botulinum toxin (**BT**) as a medical therapy did not start until 1970, and the FDA approved its use for treatment of blepharospasm and strabismus in 1989.[26]

The pathogen produces 7 antigenically distinct neurotoxins (A, B, C1, D, E, F, and G), of which type A is the most potent and most often used in clinical applications (Table 4).[25,26] The neurotoxin proteins have the ability to inhibit the release of acetylcholine from the presynaptic nerve terminal, causing local chemodenervation.[25] Toxin uptake is greater in nerve terminals that are most active, leading to weakening of the muscle fibers that are pathologically overactive.[25] These products have differences, and each should be checked before use to guarantee safety and effectiveness.[25,27]

BT type A has received FDA approval for treatment of adult patients with severe primary axillary hyperhydrosis (excessive sweating), cervical dystonia, strabismus and blepharospasm (spasm of the eyelids) associated with dystonia, and temporary improvement in the appearance of moderate to severe facial frown lines.[27] Safety and effectiveness in children younger than 12 years old have not been established for any condition.[27] Thus, in pediatric patients, all uses are off-label, even in cerebral palsy (**CP**), in which it is successfully used to reduce spasticity leading to improvements in gross motor and upper extremity function, gait patterns, and independent ambulation.[28] BT may be an alternative to orthopedic surgery for some CP children.

Other off-label uses include: hyperlacrimation; gustatory epiphora ("crocodile tears"); vasomotor rhinitis; hemifacial spasm; writer's cramp (disabling spasms of the hands while performing a job); occupational cramps (such as those seen in musicians who play string instruments); foot dystonia; essential and dystonic tremor of the neck and palate; and Parkinsonism-related hypersialorrhea; constipation; and flexion contracture.[25] In Tourette's syndrome, injection of BT in the vocal cords reduces tic frequency.[25] Bruxism can be managed with BT injections in the masseter and temporalis muscles.[25] In urology, the toxin can lead to avoidance of bladder augmentation surgery by improving incontinence through bladder paralysis.[25,29] In children, it is mostly used for incontinence that is refractory to treatment with anticholinergic medications in myelomeningocele, a type of spina bifida defect.[29] BT also has useful applications in gynecology, proctology, and gastrointestinal disorders.

Oral uses have emerged for BT. The toxin has been used successfully in the management of salivary secretory disorders, such as: "salivary fistulas"; sialoceles; recurrent parotitis; Frey's syndrome; sialorrhea; and drooling, including in pediatric patients.[30,31] BT also can treat temporomandibular disorders involving the orofacial musculature, such as: bruxism and clenching; oromandibular dystonia; myofacial pain due to parafunction and/or secondary to temporomandibular joint involvement; trismus; hypermobility; masseter and temporalis hypertrophy; and headaches.[25,32]

BT injections in therapeutic doses are safe for children and adults. There is no consensus regarding dosage, however, and the most effective dose is unknown. BT is contraindicated if infection is present at the injection site and in individuals with known hypersensitivity to any of the formulation ingredients.[27] The main limitation of the toxin is its transient effectiveness, requiring multiple and expensive administrations.[30] Antibodies against the toxin also may occur with long-term use, leading to nonresponse to the drug.[27] Adverse effects tend to be rare, mild, transient, and usually dose-dependent and result from the spread of the drug into areas adjacent to the targeted muscles.[26,29] These effects may include: dysphonia; dysarthria; dysphagia; diplopia; ptosis; flu-like symptoms; generalized muscle weakness; skin rashes; fatigue; dry mouth; reduced sweating; and constipation.[25-27] Patients should be monitored closely for atopy, and concomitant use of aminoglycoside antibiotics should be avoided because they also block neuromuscular transmission.[25,27] In cases of overdose, BT antitoxin should be considered no later than 24 hours after the BT injection.[25]

Bisphosphonates. The growing and widespread use of bisphosphonates (**BISs**) in adults has overshadowed its growing use in children. BISs strongly bind to hydroxyapatite

crystals and reduce bone resorption by inhibiting cell functions and inducing accelerated osteclast death (Table 5).[33] Osteoclasts only are affected by the superficially bound drug, and BISs buried in bone are biologically inert with a half-life of several years.[33] The drug is used to treat adults with: osteoporosis (postmenopausal and steroid-induced); hypercalcemia of malignancy; Paget's disease of bone; multiple myeloma; and skeletally-related events associated with metastatic bone disease in breast, prostate, lung, and other cancers.[34] Alternative uses include: central giant cell lesions of the jaws; giant cell tumors of the bone; fibrous dysplasia; and osteomyelitis.[34] BISs cause increased bone density in the spine, femoral neck, and tibia as well as improvements in vertebral shape.[35] They do not eliminate fracture risk, however, and are not a cure for osteogenesis imperfecta (OI).[35]

Osteoporosis has become an important issue in children and adolescents today, and BISs are being used to treat primary and secondary osteoporoses in this population.[36] The former is an intrinsic skeletal defect seen in OI, Marfan syndrome, and Ehlers-Danlos syndrome. Secondary osteoporosis is a sequelae of chronic diseases or conditions which lead to: low body mass; malnutrition or undernutrition (lack of calcium); inactivity; reduced exposure to sunlight; and hyposecretion of sexual hormones.[36] Glucocorticoids also are administered long-term to these patients, causing: increased bone resorption; impaired bone formation; reduced calcium absorption from the gut; loss of urinary calcium; and decreased sex steroid and growth hormone production.[36] BISs are used in the management of: skeletal manifestations of rheumatologic disorders; childhood cancers; anorexia nervosa; cystic fibrosis; renal failure; inflammatory bowel disease; severe burns; neurological disorders (CP, Duchenne muscular dystrophy, spinal cord injury, Rett syndrome, and prolonged immobilization for any reason); endocrine conditions (hypogonadism, Turner syndrome, diabetes mellitus, hyperthyroidism, etc); and inborn errors of metabolism (glycogen storage disease, Gaucher disease, galactosemia).[36] Lifestyle factors (eg, excessive consumption of soft drinks) also are an important consideration in secondary osteoporosis.[33]

BIS use in children remains controversial due to inadequate long-term efficacy and safety data; thus, many experts recommend limiting therapy to patients with recurrent extremity fractures, symptomatic vertebral collapse, and reduced bone mass.[35,36] There is no consensus regarding the optimal BIS agent in children, dosage, or duration of therapy which should probably be continued until growth is fully or nearly completed.[36] Pediatric patients usually tolerate the drug well. Fever, malaise, nausea, diarrhea, and muscle or bone pain are common adverse effects and tend to be mild, last only for a few days, and rarely recur with subsequent doses.[35,36] The more serious effects seen in adults, such as uveitis, thrombocytopenia, and esophageal or oral ulcerations, are rare in children.[36]

Pediatric dentists must understand the implications of treating young patients who have received or are receiving BISs. Dental care to optimize oral health and decrease the likelihood of side effects is important before, during, and after therapy. Avoiding oral surgical procedures, especially in patients who have had or are being given intravenous (**IV**) BISs, is a must. Individuals receiving oral BISs are at a considerably lower risk of BISs-related osteonecrosis of the jaws (**BRONJ**) than those who receive IV BISs.[37] There is insufficient evidence to suggest that implant placement, tooth extraction, and other surgical treatments should be routinely avoided for patients receiving oral forms of the drug. Duration of oral therapy (ie, >3 years), however, may correlate with development and severity of BRONJ.[38] BRONJ has not been reported in children to this date. As more adolescents are referred for third molar and orthodontically related extractions, however, one must carefully review the patient's medical history. Many BISs are taken every few weeks or months; thus, many patients and parents may not remember that they took it if they are not specifically asked. It is important to add such a question to the medical history form. Other medications, such as steroids, thalidomide, and chemotherapeutic agents, were initially thought to be risk factors for BRONJ, but no significant association has been shown.[37]

BISs can inhibit tooth movement, thus posing a problem for orthodontic therapy, which depends on osteoclastic activity to move teeth. It has been suggested that orthodontic treatment be avoided in patients with high risk/high level of osteoclastic inhibition, such as those who are receiving or have received IV BISs.[39] The drug also is associated with delayed tooth eruption in children with OI and with ulcers when the pills come in direct contact with the oral cavity.[40,41]

Acetylsalicylic acid. Acetylsalicylic acid (ASA, aspirin) has been used clinically for more than 100 years and is enjoying a rebirth for its benefits in several pediatric and adult conditions. Its antiplatelet effect was recognized approximately 40 years ago. To this day, it remains the leading drug in the management of thrombosis and cardiovascular disorders.[42] Despite new developments in antiplatelet drugs such as adenosine diphosphate receptor inhibitors and glycoprotein IIb/IIIa inhibitors, it is highly unlikely that they will provide the broad therapeutic index observed with ASA, including the anti-inflammatory and immunomodulatory actions.[42]

Platelets are essential to the preservation of vascular integrity and the control of bleeding at sites of injury. They promote fibrin formation, clot retraction, and fibrinolysis, recruit inflammatory cells to the thrombus, and initiate repair of the injured vessel walls.[43] They also can contribute to the development of atherosclerotic plaques, which become foci for the formation of platelet thrombi, causing arterial occlusion and ischemic injury to vital organs, mainly myocardial infarction and stroke.[43,44] ASA has the capacity to inactivate the cyclo-oxygenase (**COX**) activity of prostraglandin H -synthase 1 and 2 (COX-1 and -2, respectively).[44] Inhibition of COX-1-dependent platelet function (eg, aggregation and vasoconstriction) can be done with a daily low dose of ASA, while inhibition of COX-2-dependent pathophysiologic processes (such as hyperalgesia and inflammation) requires larger doses and a much

shorter dosing interval.[44] Peak plasma levels occur 30 to 40 minutes after ASA ingestion, and inhibition of platelet function is evident within 1 hour (3 to 4 hours for enteric-coated aspirin).[44] Despite its short half-life of 15 to 20 minutes, the platelet inhibitory effect of ASA lasts the lifespan of the platelet (8-10 days) because the drug irreversibly inactivates COX-1. ASA is an effective antithrombotic agent in doses between 50 and 1,500 mg/day.[44]

Advances in the care of critically ill children have led to an increased incidence of thromboembolic disease in this population. Evidence for the use of antiplatelet therapy in children is very limited, however, and usually is extrapolated from experience with adult patients.[43] The most common indications for the use of ASA and other antiplatelet drugs in children include: ischemic stroke (due to congenital heart disease, sickle cell disease, vasculopathies, vasculitis, infection, metabolic disease, and congenital or acquired thrombophilia); Kawasaki disease; and cardiac surgery (placement of mechanical prosthetic valves and endovascular stents, Blalock-Taussig shunts, Fontan procedure, etc).[43]

An adverse effect of ASA is gastrointestinal toxicity, even when administered at low doses or even in its enteric-coated form.[44] Salicylates are present in numerous over-the-counter products, including aspirin, oil of wintergreen, and Pepto-Bismol (Procter and Gamble, Cincinnati, Ohio). Because it is not widely known that these products contain salicylates, significant toxicity may not be recognized initially as salicylate ingestion.[45] The minimal potentially toxic ingested dose in children is 150 mg/kg. Signs and symptoms of toxicity may occur at levels greater than 30 mg/dL and include nausea, vomiting, hyperventilation, hyperpnea, tinnitus, and nonspecific neurologic findings such as agitation, delirium, hallucinations, and lethargy.[45] Despite widespread belief that ASA intake can lead to Reye syndrome, there is not one study that has established a causal relationship.[46] Today, most Reye-like syndromes can be described as inborn errors of metabolism without any direct relationship to ASA. Because of this myth, ASA has been replaced with acetaminophen, which bears a significant hepatotoxicity potential and may have led to a worldwide increase in several allergic diseases, most notably asthma, because it lacks anti-inflammatory activity.[46] Furthermore, frequent acetaminophen use can cause asthma attacks.

Interruption of antithrombotic and antiplatelet therapy exposes patients to an increased risk for thromboembolic events, which can lead to devastating clinical consequences including major disability and even death.[47] The guidelines of the American College of Chest Physicians state that patients undergoing minor dental procedures who are receiving ASA should continue it around the time of surgery because of the low risk of postoperative oral bleeding complications resulting from those procedures, including extractions.[47] ASA rarely causes significant hemorrhage, except in the presence of an underlying hemostatic defect or in children also treated with anticoagulants or thrombolytic therapy.[44,48]

Guidelines also suggest against routine use of platelet function assays to monitor ASA's antithrombotic effect. Therefore, it is clear that pediatric dentists can proceed with oral surgical procedures in children and adolescents taking aspirin without any modification of care. The pediatric dentist should also clarify with the child's physician that ASA can indeed be continued, as some may assume that it will lead to excessive bleeding from dental procedures and order the patient to stop it. Anesthesiologists often erroneously defer nasal intubation in these patients unless the drug has been stopped for a few days prior to surgery, thus prolonging and complicating dental care under general anesthesia.

Summary

The purpose of this paper was to identify several areas in which existing, often well-known medications with clearly defined purposes have been employed to manage different conditions and diseases in children. While clearly beneficial to the child's health, these drugs may present side effects that manifest in the oral cavity. Pediatric dentists need to stay current with advances in pediatric medicine because many of these medications have unexpected effects, such as bleeding or immune suppression, which can affect oral health and dental care delivery.

References

1. Landmark CJ. Antiepileptic drugs in nonepilepsy disorders. Relations between mechanisms of action and clinical efficacy. CNS Drugs 2008;22:27-47.
2. Ettinger AB, Argoff CE. Use of antiepileptic drugs for nonepileptic conditions: Psychiatric disorders and chronic pain. Neurotherapeutics 2007;4:75-83.
3. Kelleher KJ, McInerny T, Gradner WP, Childs GE, Wasserman RC. Increasing identification of psychosocial problems: 1979-1996. Pediatrics 2000;105:1313-21.
4. McElroy SL, Guerdjikova AI, Martens B, Keck PE Jr, Pope HG, Hudson JI. Role of antiepileptic drugs in the management of eating disorders. CNS Drugs 2009;23: 139-56.
5. Cordas TA, Tavares H, Calderoni DM, Stump GV, Ribeiro RB. Oxcarbazepine for self-mutilating bulimic patients. Int J Neuropsychopharmacol 2006;9:769-71.
6. Michaelis M, Doerr HW, Cinatl J Jr. Valproic acid as anti-cancer drug. Curr Pharmacol Design 2007;13: 3378-93.
7. Teo SK, Stirling DI, Zeldis JB. Thalidomide as a novel therapeutic agent: New uses for an old product. Drug Discov Today 2005;10:107-14.
8. Melchert M, List A. The thalidomide saga. Int J Biochem Cell Biol 2007;39:1489-99.
9. Rosenbach M, Werth VP. Dermatologic therapeutics: Thalidomide. A practical guide. Dermatol Ther 2007;20: 175-86.
10. Kari JA, Shah V, Dillon MJ. Behçet's disease in UK children: Clinical features and treatment including thalidomide. Rheumatol 2001;40:933-8.
11. Prins C, Gelfand EW, French LE. Intravenous immunoglobulin: Properties, mode of action, and practical use in dermatology. Acta Derm Venereol 2007;87:206-18.

12. Udi N, Yehuda S. Intravenous immunoglobulin: Indications and mechanisms in cardiovascular diseases. Autoimmun Rev 2008;7:445-52.
13. Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immune globulin and the rationale behind it: The Massachusetts General Hospital data and a review of the literature. Transfusion 2006;46:741-53.
14. Looney RJ, Huggins J. Use of intravenous immunoglobulin G (IVIG). Best Pract Res Clin Haematol 2006;19:3-25.
15. Leong H, Stachnik J, Bonk ME, Matuszewski KA. Unlabeled uses of intravenous immune globulin. Am J Health-Syst Pharm 2008;65:1815-24.
16. Brawley OW, Cornelius LJ, Edwards LR, et al. National Institutes of Health Consensus Development Conference statement: Hydroxyurea treatment for sickle cell disease. Ann Intern Med 2008;148:932-8.
17. De Benedittis M, Petruzzi M, Giardina C, Lo Muzio L, Favia G, Serpico R. Oral squamous cell carcinoma during long-term treatment with hydroxyurea. Clin Exp Dermatol 2004;29:605-7.
18. Strouse JJ, Lanzkron S, Beach MC, et al. Hydroxyurea for sickle cell disease: A systematic review for efficacy and toxicity in children. Pediatrics 2008;122:1332-42.
19. Khatib R, Rabah R, Sarnaik SA. The spleen in the sickling disorders: An update. Pediatr Radiol 2009;39:17-22.
20. da Fonseca MA, Oueis HS, Casamassimo P. Sickle cell anemia: A review for the pediatric dentist. Pediatr Dent 2007;29:159-69.
21. Said S, Jeffes EWB, Weinstein GD. Methotrexate. Clin Dermatol 1997;15:781-97.
22. Niehues T, Lankisch P. Recommendations for the use of methotrexate in juvenile idiopathic arthritis. Paediatr Drugs 2006;8:347-56.
23. Federal Drug Administration. Available at: "www.accessdata.fda.gov/drugsatfda_docs/label/2004/1171951r106_methotrexate_lbl.pdf". Accessed July 21, 2009.
24. Kalantzis A, Marshman Z, Falconer DT, Morgan PR, Odell EW. Oral effects of low-dose methotrexate treatment. Oral Surg Oral Med Oral Pathol Radiol Endod 2005;100:52-62.
25. de Maio M. Therapeutic uses of botulinum toxin: From facial palsy to autonomic disorders. Expert Opin Biol Ther 2008;8:791-8.
26. Erbguth FJ. From poison to remedy: The chequered history of botulinum toxin. J Neural Transm 2008;115:559-65.
27. Federal Drug Administration. Available at: "www.accessdata.fda.gov/drugstafda_docs/label/2004/103000s5050lbl.pdf". Accessed July 24, 2009.
28. Nolan KW, Cole LL, Liptak GS. Use of botulinum toxin type A in children with cerebral palsy. Phys Ther 2006;86:573-84.
29. DasGupta R, Murphy FL. Botulinum toxin in paediatric urology: A systematic literature review. Pediatr Surg Int 2009;25:19-23.
30. Capaccio P, Torretta S, Osio M, et al. Botulinum toxin therapy: A tempting tool in the management of salivary secretory disorders. Am J Otolaryngol 2008;29:333-8.
31. Pena AH, Cahill AM, Gonzalez L, Baskin KM, Kim H, Towbin RB. Botulinum toxin A injection of salivary glands in children with drooling and chronic aspiration. J Vasc Interv Radiol 2009;20:368-73.
32. Schwartz M, Freund B. Treatment of temporomandibular disorders with botulinum toxin. Clin J Pain 2002;18:S198-S203.
33. Bianchi ML. How to manage osteoporosis in children. Best Pract Res Clin Rheumatol 2005;19:991-1005.
34. Landesberg R, Eisig S, Fennoy I, Siris E. Alternative indications for bisphosphonate therapy. J Oral Maxillofac Surg 2009;67(suppl 1):27-34.
35. Castillo H, Samson-Fang L. Effects of bisphosphonates in children with osteogenesis imperfecta: An AACPDM systematic review. Develop Med Child Neurol 2008;51:17-29.
36. Bachrach LK, Ward LM. Clinical review: Bisphosphonate use in childhood osteoporosis. J Clin Endocrinol Metab 2009;94:400-9.
37. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons position paper on a bisphosphonate-related osteonecrosis of the jaws: 2009 update. J Oral Maxillofac Surg 2009;67(suppl 1):2-12.
38. Grant BT, Amenedo C, Freeman K, Kraut RA. Outcomes of placing dental implants in patients taking oral bisphosphonates: A review of 115 cases. J Oral Maxillofac Surg 2009;66:223-30.
39. Zahrowski JJ. Bisphosphonate treatment: An orthodontic concern calling for a proactive approach. Am J Orthop Dentofacial Orthop 2007;131:311-20.
40. Kamoun-Goldrat A, Ginisty D, Le Merrer M. Effects of bisphosphonates on tooth eruption in children with osteogenesis imperfecta. Eur J Oral Sci 2008;116:195-8.
41. Gonzalez-Moles MA, Bagan-Sebastian JV. Alendronate-related oral mucosa ulcerations. J Oral Pathol Med 2000;29:514-8.
42. Fareed J, Hoppensteadt DA, Fareed D, et al. Survival of heparins, oral anticoagulants, and aspirin after the year 2010. Semin Thromb Hemost 2008;34:58-73.
43. Israels SJ, Michelson AD. Antiplatelet therapy in children. Thromb Res 2006;118:75-83.
44. Patrono C, Baigent C, Hirsh J, Roth G. Antiplatelet drugs. American College of Chest Physicians evidence-based clinical practice guidelines. 8th ed. Chest 2008;133:199S-233S.
45. Michael JB, Sztajnkrycer MD. Deadly pediatric poisons: Nine common agents that kill at low doses. Emerg Clin N Am 2004;22:1019-50.
46. Schör K. Aspirin and Reye syndrome: A review of the evidence. Paediatr Drugs 2007;9:195-204.
47. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy. American College of Chest Physicians evidence-based clinical practice guidelines. 8th ed. Chest 2008;133:299S-339S.
48. Monagle P, Chalmers E, Chan A, et al. American College of Chest Physicians evidence-based clinical practice guidelines. 8th ed. Chest 2008;133:887S-968S.