USEFUL DRUG & DENTAL MANAGEMENT REFERENCES

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I. PROPERTIES OF THE IDEAL DRUG REFERENCE

- **Comprehensive** - index lists brand and generic names of all drugs marketed in country of choice
- **Comparative** - includes tables of drug categories vs. side effects, kinetics, interactions, spectrum of action for antimicrobials and clinical characteristics for analgesics
- **Complete** - includes both prescription AND OTC medications in U.S. and Canada

II. GENERAL DRUG REFERENCE SOURCES

A. DRUG FACTS AND COMPARISONS (DFC)-www.factsandcomparisons.com
-pocket edition is $69.95, loose leaf is $429 with renewals at $389, Drug Interactions Facts is $235/$89.95
-2015 annual hardcover edition (no monthly updates) is $215/year/22,000 Rx, 6000 OTC drugs
-2015-available for PDA called A to Z Drug Facts for PDA/Pocket PC,SmartPhone

B. LEXI-COMP DRUG INFORMATION HANDBOOK FOR DENTISTRY – www.lexi.com
-2015 Handbook 20th ed. (May-June) is $69.95, available for one or more office PCs as well
-2015PDA/Blackberry,Android,iPhone,iPad,iTouch,,HP,PocketPC,PalmOS:**Dental Lexi Drugs is $75/year**

III. SPECIFIC DENTAL DRUG RESOURCES

A. GUIDE TO ANTIMICROBIAL THERAPY 2015 (June every year) – www.sanfordguide.com
-desktop, spiral bound, softcover, PDA/Pocket PC versions available
-Spiral is $29.95, softcover is $12.50, PDA/Pocket PC are $29.95

B. PEDIATRIC DRUG DOSAGE HANDBOOKS

1. Harriet Lane Handbook: 20th Edition. $ 59.95 Mosby. 2015
2. Pediatric Lexi-Drugs for Blackberry by Lexi-Comp
3. Pediatric Dosage Handbook 21st edition, $69.95 by Lexi-Comp 2014-2015

C. ANXIOLYSIS AND CONSCIOUS SEDATION HANDBOOKS

1. Malamed Stanley. Sedation: A Guide to Patient Management. 5th edition, 2010, C.V. Mosby ($69.95)
2. **Handbook of Nitrous Oxide and Oxygen Sedation. 4th edition, Mosby ($66.95)**

D. DENTAL MANAGEMENT GUIDES

1. **Malamed Stanley. Medical Emergencies in the Dental Office. 7th edition. 2014 (99.95)**
2. **Little and Falace. Dental Management of the Medically Compromised Patient. 8th edition. April 2012 (72.95)**
3. **Malamed Stanley. Handbook of Local Anesthesia. 6th edition, April 2012. (72.95)**

IV. Herbal and Nutritional Drug Product References

A. Natural Medicines Comprehensive Database – www.naturaldatabase.com
-best resource for health professionals but priced at $299/year so may be too expensive

B. Nutrition Action Health Letter – www.cspinet.org
-published by Center for Science in the Public Interest (CSPI) - $24/10 issues per year

C. Other Useful Websites
-www.consumerlab.com, www.quackwatch.com, www.mskcc.org/mskcc/html/11570.cfm., www.ific.org
-www.science-basedmedicine.org. www.supplement-geek.com with author Joe Cannon, M.S.

NEW STRATEGIES FOR TARGETING ANTIBIOTIC USE IN CLINICAL DENTISTRY

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I. TARGETED INDICATIONS IN DENTAL PRACTICE

A. Therapeutic Indications

1. Acute cellulitis of dental origin
2. Acute pericoronitis with elevated temperature and trismus
3. Deep fascial space infections
4. Open fractures of the mandible and maxilla
5. Extensive, deep, or old (>6hours) orofacial lacerations
6. Dental infection or oral surgery in the compromised host

B. Prophylactic Indications

1. Valvular heart disease
2. Prosthetic heart valve
3. Intravascular access device in place
4. Prosthetic joint replacement (first two years)

II. TARGETED PATIENTS AT INCREASED RISK OF OROFACIAL INFECTIONS

A. Patient-Specific Risk Factors

1. Immunocompromised by drug therapy or disease process
   a. drug therapy – methotrexate, cyclophosphamide, prednisone hydroxychloroquine, cyclosprine A, etc.

   b. disease process – SLE, rheumatoid arthritis, malnutrition, neoplastic disease, poor glycemic control in diabetics (A1c > 8%)

2. Impaired by trauma, surgery, reduced circulation, or implanted device
   a. hematomas and scar tissue – promote bacterial proliferation
   b. reduced circulation – may prevent antibiotic from reaching site
   c. implanted devices – intravascular devices are the leading cause of nosocomial infections and increase risk of endocarditis in some cases

3. Renal Insufficiency

   a. Tetracycline and minocycline are contraindicated in renal failure
   b. Dosage reduction necessary for amoxicillin, cefuroxime, cephalexin, and fluoroquinolones
   c. No dosage reduction necessary for azithromycin, cefaclor, clindamycin, dicloxacillin, doxycycline, erythromycin, metronidazole

4. Diabetic Glycemic Control

Correlation Between A1c and Mean Plasma Glucose

A1c (%)	Mean plasma glucose	
6	126mg/dl	
7	154mg/dl	
8	183mg/dl	
9	212mg/dl	⇦ **Patient Risks Increased**
10	240mg/dl	
11	269mg/dl	
12	298mg/dl	

Importance of Glycemic Control in Dental Patients

Prevention of hyperglycemia
Nonketotic hypertonicity/ketoacidosis
Impaired wound healing
Increased risk of oral infection
Delayed gastric emptying could lead to aspiration during a procedure
Prevention of hypoglycemia

5. Medico Legal Issues in Antibiotic Prescribing-**JADA April 2004 and January 2012**

Reasons Why Antibiotics Fail

- Inadequate drainage or debridement
- Antibiotic does not reach infection site
- Physical obstruction or open access
- Systemic disease alters host response
- Foreign body reaction
- Patient noncompliance
- Inadequate dose or duration
- Wrong antibiotic is chosen
- Development of bacterial resistance
- Concomitant therapy interferes

Pitfalls in Antibiotic Prescribing

- Antibiotic adverse effects not considered
- Cost of antibiotic not considered
- Rapid and inappropriate therapy changes
- Patient is not counseled or monitored
- Trying to treat viral infections
- Inappropriate drug or dosage selection
- Infecting agent not documented
- Failure to correct contributing factors

III. TARGETED ANTIBIOTIC SELECTION

A. Mechanism of action and spectrum of activity

BACTERIOSTATIC	*BACTERICIDAL*	*SPECTRUM OF ACTIVITY*		
		Narrow	**Extended**	**Broad**
Tetracyclines	Penicillins	Penicillin VK	Amoxicillin	Tetracyclines
Sulfonamides	Cephalosporins	Erythromycin	Cephalosporins	Sulfonamides
Macrolides	Metronidazole	Clindamycin	Fluoroquinolones	
Clindamycin(static/Cidal)	Fluoroquinolones	Metronidazole		

B. Activity Against Common Oral Pathogens

Aerobic Bacteria	Frequency	Anaerobic Bacteria	Frequency
Gram-positive cocci		Gram-positive cocci	
Streptococcus		Peptostreptococcus	common
Viridans	very common		
B-Hemolytic	unusual	Gram-negative bacilli	
Staphylococcus	rare	Porphyromonas (Bacteroides)	rare
		Prevotella (Bacteroides)	very common
		Fusobacterium	common
		Bacteroides fragilis	rare

1. The typical odontogenic infection is composed of a mix of aerobic and anaerobic species
2. The timeline of infection may show: AEROBES-------MIXED-------ANAEROBES.
3. Obtain cultures & sensitivities for: antibiotic failures, recalcitrant infections, suspected osteomyelitis, impaired host defenses, post-op wound infections, etc.

IV. ANTIBIOTIC THERAPY GUIDELINES

A. Antimicrobial prescribing in the USA is 80 % empirical therapy.

1. Target causative organism -empirical or lab
2. Patient drug and medical history - ALLERGIES vs ADVERSE REACTIONS??
3. Patient counseling - adverse effects, compliance, therapeutic endpoints, cost
4. Positive response expected in 48 hours, continue therapy 72 hours after symptom resolution
5. Combination therapy: 3 possible effects - indifferent (additive) - synergism – antagonism
   Cidal + Cidal *or* Static + Static
6. Best combination: penVK qid + metronidazole qid, or amoxicillin tid + metronidazole tid

V. ANTIBIOTIC CLASSES

A. ORAL PENICILLINS – FDA Pregnancy Category B

ORAL PENICILLINS USEFUL IN DENTISTRY

Classification	$t^{1}/_{2}$ (h)	OK with food?	Pediatric Dose	Activity against oral pathogens Gm^{+} Aerobes	Gm^{+} Anaerobes	Gm^{-} Anaerobes
Natural						
Penicillin G	1	no	150-250K U/kg/d	+	+	+
Penicillin VK	1	yes	25-50mg/kg/day	+	+	+,-
Penicillinase-Resistant						
Dicloxacillin	.75	no	12-25mg/kg/day	staph only	-	-
Nafcillin	.75	no	37mg/kg q 6h	staph+strep	-	-
Aminopenicillins						
Amoxicillin	1.5	yes	40-50mg/kg/day	+	+	-
Amox/potassium clavulanate(Augmentin,G)	1.5	yes	40-45mg/kg/day	+	+	+
Ampicillin	1.5	no	50-100mg/kg/day	+	-	+,-

1. INDIVIDUAL AGENTS

Amoxicillin advantages over penicillin
- more complete absorption
- longer duration of activity
- TID administration

Amoxicillin disadvantages over Pen VK
-broader spectrum
-poor anaerobe activity
-more side effects/less efficacy

2. ADVERSE EFFECTS

Hypersensitivity

- 3 - 10 % of population is allergic to penicillins (more frequently with IV/IM than PO route)
- IgE Mediated acute reaction - PCN binds to protein and acts as a hapten to which Ab develop
- True anaphylactic reactions to penicillin are 1/7,000 to 1/25,000 instances of PCN use
  - *mortality occurs once in every 50,000 - 60,000 treatment courses
  - * sx. begin 10-20 min. after ingestion, antihistamines are of little effect
- Cross-reactivity to cephalosporins occurs in 3-5% of patients
  - *Cephalosporins are contraindicated with pt history of severe or immediate penicillin reaction (urticaria, angioedema, anaphylaxis)

3. DRUG INTERACTIONS

Bacteriostatic antibiotics
Oral contraceptives
Methotrexate

B. ORAL CEPHALOSPORINS – FDA Pregnancy Category B

Oral Cephalosporins Useful in Dentistry

Classification	$t^1/_2$ (min)	OK with food?	Pediatric Dose	activity against oral pathogens: Gm^+ Aerobes	Gm^+ Anaerobes	Gm^- Anaerobes
First Generation						
Cephalexin (Keflex,g)	50-80	yes	25-50mg/kg/d (4)	+	-	-
Cefadroxil(Duricef,Ultracef,g)	78-96	yes[1]	30mg/kg/day (1)	+	-	-
Cephradine(Anspor,Velosef,g)	48-80	yes	25-50mg/kg/day (4)	+	-	-
Second Generation						
Cefaclor (Ceclor,G)	35-54	yes	20-40mg/kg/day (3)	+	+	+
Cefuroxime (Ceftin,G))	80	yes[1]	10-15mg/kg bid (2)	+	+	+,+
Cefprozil (Cefzil,G)	78	yes[+]	15-30mg/kg/day (2)	+	+	+
Loracarbef (not available now)	60	no	15-30mg/kg/day (2)	+	+	+
Third Generation						
Cefdinir (Omnicef)	100	yes	14mg/kg/day (1-2)	+	-	-
Cefixime (Suprax)	180-240	yes	8mg/kg/day (1-2)	+	-	-
Cefpodoxime (Vantin)	120-180	yes[+]	10mg/kg/day (2)	+	+	-
Ceftibuten (Cedax)	144	no	4.5mg/kg bid	+,-	-	-
Cefditoren (Spectracef)	96	yes	None given	+++	-	+,-

1. INDIVIDUAL AGENTS

1st generation: best gram + coverage of all cephalosporins
2nd generation: best anaerobe coverage of all cephalosporins
3rd generation: oral agents provide NO oral anaerobe activity

2. ADVERSE EFFECTS

Hypersensitivity
Oral candidiasis

3. DRUG INTERACTIONS

Bacteriostatic antibiotics
Anticoagulants
Antacids, H_2 blockers, PPIs (cefdinir, cefuroxime)

C. ORAL MACROLIDES – FDA Pregnancy Category B (except Biaxin)

Oral Macrolides Useful in Dentistry						
Drug	Tpeak(h)	OK with food?	Pediatric Dose	activity against oral pathogens Gm⁺ Aerobes	Gm⁺ Anaerobes	Gm⁻ Anaerobes
Erythromycin Base						
Abbott Filmtab	3	no	30-40mg/kg/day	+	-	-
Boots E-Mycin (EC)	6	yes	(3-4)	+	-	-
Abbott Ery-Tab (EC)	3f, 2nf	yes	(3-4)	+	-	-
Abbott PCE (PC)	3	no?	(3-4)	+	-	-
P-D ERYC (EC)	3	no	(3-4)	+	-	-
Erythromycin Ethylsuccinate						
Abbott E.E.S., generic	2	yes	Base dose x 1.6	+	-	-
Erythromycin Stearate						
Abbott Erythrocin	3	no	30-40mg/kg/day	+	-	-
Azithromycin (Zithromax,g)	2-3	Caps-no Tabs-yes	Day 1: 10mg/kg Days 2-5: 5mg/kg	+	+,-	+,-
Clarithromycin (Biaxin,g) Preg C	1.7	yes	15mg/kg/day (1-2)	+	+,-	+
Dirithromycin (Dynabac,g)	6	yes	Not given	+	-	-

1. INDIVIDUAL AGENTS

Clarithromycin (Biaxin) advantages over erythromycin base:

- 3% GI irritation as opposed to 30% for older agents, BID dosing
- better activity against *S. pyogenes* than erythromycin, cefaclor or doxycycline
- better anaerobe coverage than erythromycin
- pregnancy C classification by FDA

Azithromycin (Zithromax): 2-4 fold less active than erythromycin against most strains of strep.,no risk of QT interval prolongation. Azalide has limited drug interactions compared to macrolides

Dirithromycin (Dynabac): same as erythromycin base but once daily

2 ADVERSE EFFECTS

Cholestatic jaundice (estolate salt = Ilosone)
Gastrointestinal disturbances
Taste disturbances (Clarithromycin)
Oral candidiasis

3. DRUG INTERACTIONS

Alfentanil	Carbamazepine	Ergotamine
Anticoagulants	CCBs (diltiazem, verapamil)	"Statins"
Azole antifungals	Cyclosporine	Theophylline
Bromocriptine	Disopyramide	Tolterodine

D. ORAL FLUOROQUINOLONES – FDA Pregnancy Category C

Oral Fluoroquinolones Available in the USA						
Drug*	$t^{1}/_{2}$ (h)	OK with food?	Usual Adult Dose	activity against oral pathogens Gm⁺ Aerobes	Gm⁺ Anaerobes	Gm⁻ Anaerobes
Ciprofloxacin (Cipro, G)	5	yes	500mg bid	-	-	-
Gemifloxacin (Factive,G)	7	yes	320mg qd	+	+	+,-
Levofloxacin (Levaquin,G)	8	yes	500mg q24 h	++	+	-
Moxafloxacin (Avelox,G)	10	yes	400mg qd	+	+	+,-
Norfloxacin (Noroxin)	6	no	400mg q 12h	-	-	-
Ofloxacin (Floxin)	8	yes	400mg q12h	+,-	+	-

*not indicated for children or adolescents except for cystic fibrosis

1. ALL FLUOROQUINOLONES HAVE A BLACK BOX WARNING FOR ACHILLES TENDON RUPTURE!!

2. ADVERSE EFFECTS

Arthropathies: contraindicated for children, adolescents, pregnant or lactating women
CNS stimulation/toxicity
Gastrointestinal disturbances
Photosensitivity-worst with sparfloxacin
QT interval prolongation risk

3. DRUG INTERACTIONS

Antacids (Fe, sucralfate, zinc)
Antiarrhythmics (Spar)
Anticoagulants
Antineoplastics
Cimetidine
Cyclosporine
NSAIDS (increased CNS stimulation)
Probenecid
Theophylline
Caffeine (Cipro)

E. MISCELLANEOUS AGENTS

Miscellaneous Oral Agents

Drug	$t^1/_2$ (h)	OK with food?	Pediatric Dose	activity against oral pathogens Gm$^+$ Aerobes	Gm$^+$ Anaerobes	Gm$^-$ Anaerobes
Clindamycin (Cleocin,g) FDA B	2	yes	15-30mg/kg/day (3-4)	+	+	+
Metronidazole (Flagyl,g) FDA B	8	yes	30mg/kg/day (3-4)	-	+	+
Tetracyclines FDA D						
Tetracycline HCL(Sumycin,g)	6-12	no	25-50mg/kg/d (4)	-	+	+,-
Doxycycline (Vibramycin,g)	15-25	yes	2-4mg/kg/day (2)	-	+	+,-
Minocycline (Minocin,g)	11-18	yes	4mg/kg x 1 day, 2mg/kg/day	-	+	+,-

1. CLINDAMYCIN is Pregnancy Category B

a). Cross-reaction with erythromycins because they are all "mycins"??
b). Adverse effects:
Gastrointestinal disturbances
Morbilliform skin eruptions
c)BLACK BOX WARNING: ***Clostridia Difficile Induced Colitis (CDIC)***
caused by overgrowth of Clostridia difficile which produces a toxin
Four requirements for CDIC:
1. Presence of Clostridia difficile in GI tract
2. Altered gastrointestinal flora
3. Presence of Toxin A and B
- must have toxin receptors in gut
4. Predisposing factors

* potential adverse effect of all antimicrobial agents - especially ones that affect obligate anaerobes (ampicillin, Augmentin, cephalosporins)
* S/Sx: profuse, watery diarrhea 1-20 times/day, bloody diarrhea in 5-10 % of cases, foul smelling, abdominal cramping, nausea, fever and leukocytosis
* risk factors: recent hospitalization, recent broad-spectrum antibiotic use, history of colitis, advanced age, recent instrumentation of lower bowel

* may occur up to 10 weeks after discontinuation of the antimicrobial agent
d). Drug interactions
Succinylcholine Erythromycin Kaolin-Pectin

2. METRONIDAZOLE

a.) **BLACK BOX WARNING**: Metronidazole has been shown to be carcinogenic when given chronically to rats and mice. Avoid use in children except for approved indication (amebiasis).

b.) Adverse effects – taste disturbances, peripheral neuropathy, GI irritation
- mutagenic effect demonstrated with in vitro assays as well

c.) Interaction with ethanol and disulfuram (Antabuse) may lead to gastrointestinal distress and N/V. Avoid alcohol during and for 1 day after discontinuing metronidazole.Preg Category B

d). Drug interactions

Anticoagulants	Disulfuram	Ethanol (IV diazepam, IV SMZ/TMP)
Lithium	Phenytoin	

3. TETRACYCLINES

a). Adverse effects
Esophageal ulceration
Toxicity -outdated tetracycline
Pregnancy – hepatotoxicity. Pregnancy Category D due to pediatric tooth discoloration

b). Drug interactions

ALL TETRACYLINES	*DOXYCYCLINE*	*TETRACYCLINE*
Antacids, bismuth	Phenobarbital	Food (milk, dairy)
Iron salts	Phenytoin	Cholestipol
Oral contraceptives		Zinc sulfate

c). Periodontal infections
Advantages in periodontal infections:
- high concentration in GCF
- good activity against A.A
- binds to root surfaces
- anticollagenase activity

d). Periodontal abscesses – tetracyclines are NOT the drugs of choice

e). Compliance considerations: cost, GI irritation, doses per day

4. OXALODINONES – Linezolid (Zyvox) 400mg and 600mg tablets
a) reserved for resistant gram positive pneumonias and CA-MRSA
b) NOT effective for oropharyngeal anaerobes

F. PATIENT-SPECIFIC ANTIBIOTIC SELECTION CRITERIA

1. History of allergy to penicillin
   a. Avoid all penicillins
   b. Avoid cephalosporins if hives, angioedema, anaphylaxis, or unknown history is reported

2. History of antibiotic-associated diarrhea
   a. Use narrow spectrum agent if possible-consider flora support with Florajen3 probiotic supplement Best choice is pen VK with /without metronidazole
   b. Avoid 2nd and 3rd generation cephalosporins
   c. Avoid clindamycin and amoxicillin/clavulanic acid (Augmentin,G)

3. Inadequate response to penicillin VK
   a. Add metronidazole 1000-2000mg/day in four divided doses to pen VK
   b. Stop pen VK and initiate clindamycin 300mg qid or q 6h.
   c. Stop pen VK and initiate Augmentin 500/125 tid or q 8h.

4. Allergy or intolerance to penicillins, cephalosporins, macrolides, clindamycin
   a. Reserve agents include levofloxacin or moxafloxacin
   b. May combine fluoroquinolone with metronidazole for resistant anaerobic infections

5. Patient may be pregnant
   a. Use penicillins, cephalosporins, clindamycin
   b. Avoid clarithromycin, all fluoroquinolones and tetracyclines
   c. Macrolides may be too hard on gut

Cellulitis versus Abscess

• Acute	• Chronic
• More painful	• Less painful
• Large and widespread	• Localized, well-defined
• Soft to very hard (board-like)	• Fluctuant
• Can be very dangerous in advanced stages	• Less dangerous
• Pus absent	• Pus present
• Aerobic	• Anaerobic

General Dentist or Specialist?

Criteria for referral to a specialist:

- Rapidly progressive infection
- Difficulty in breathing
- Difficulty in swallowing
- Fascial space involvement
- Elevated temperature (greater than 101°F)
- Severe Trismus (less than 10 mm)
- Toxic appearance
- Compromised host defenses

Targeted Antibiotic Selection

- Mechanism of Action
  - Cidal better than static
- Spectrum of Activity
  - Narrow better than extended
- Activity Against Oral Pathogens
  - Strep Viridans
  - Peptostreptococcus
  - Porphyromonas, Prevotella
  - Fusobacterium

Uncomplicated Odontogenic Infections Usually **DO NOT** Require Antibiotics

- Reversible or Irreversible Pulpitis
- Acute Apical Periodontitis
- Draining Sinus Tract
- Gingival or Periodontal Abscess
- ANUG or NUG
- Alveolar Osteitis
- Localized Pericoronitis

Steps in Appropriate Odontogenic Infection Antibiotic Prescribing

- Establish a clear indication of need
  - Patient presents with malaise, fever, chills, trismus, rapid respirations, swelling, lymphadenopathy, or hypotension
    - Signs of infection have escalated rapidly over the past 24 to 48 hours
    - Oral soft tissue swelling appears to be spreading
    - Patient presents with signs of impending airway obstruction: marked trismus (<25mm), dehydration, malaise, disorientation, tachycardia, and hypotension SHOULD BE ADMITTED TO THE HOSPITAL for urgent care
- Determine the Patient's Health Status
  - Systemic Considerations
  - History of Adverse Drug Reactions
  - Potential Drug-Drug Intx

Steps in Appropriate Antibiotic Prescribing

- Select appropriate agent with narrow spectrum and acceptable adverse effects for individual patient
  - Immune status of patient determines static vs cidal
  - Empiric therapy based on most likely organisms associated with odontogenic infections
  - Culture and sensitivity testing if patient compromised or resistance suspected
- Establish a dosage regimen
  - Consider infection severity and specific compliance issues
- Follow up in 48 hours to check efficacy
  - Reasons why antibiotics fail
  - Monitor patient for adverse effects

Antimicrobial Adult Regimens for Odontogenic Infections

PENICILLINS

NAME	USUAL DOSAGES	USUAL REGIMENS
PENICILLIN VK (generic)	**Tablet**: 250MG, 500MG	500MG TAB QID OR Q 6 HOURS UNTIL GONE.
AMOXICILLIN (generic)	**Capsules**: 250MG,500MG **Tablets**:250MG CHEWABLE **Tablets**: 875MG	500MG CAP TID OR Q 8 HOURS UNTIL GONE.
AMOXICILLIN/POTASSIUM CLAVULANATE (AUGMENTIN,G)	**Tablets**: 250 mg amoxicillin with 125 mg clavulanate, 500 mg amoxicillin with 125 mg clavulanate, 875 mg amoxicillin with 125 mg clavulanate.	500MG/125MG TID OR Q 8 HOURS UNTIL GONE.

CEPHALOSPORINS

NAME	USUAL DOSAGES	USUAL REGIMENS
Cefaclor (Ceclor, generic)	**Capsule**: 250 MG, 500 MG **Powder for Suspension**: 125 MG/5 ML, 187 MG/5 ML, 250 MG/5 ML, 375 MG/5 ML **Tablet, Extended Release**: 500 MG	250mg-500mg TID OR Q 8 HOURS UNTIL GONE.
Cefuroxime (Ceftin, generic)	**Powder for Suspension**: 125 MG/5 ML, 250 MG/5 ML **Tablet**: 125 MG, 250 MG, 500 MG	250mg-500mg BID OR Q 12 HOURS UNTIL GONE.
Cefazil (Cefzil,generic)	**Powder for Suspension**: 125 MG/5 ML, 250 MG/5 ML **Tablet**: 250 MG, 500 MG	250mg-500mg BID OR Q 12 HOURS UNTIL GONE.
Loracarbef (Lorabid)	**Capsules:** 200mg, 400mg **Powder for Suspension:**100mg/5ml, 200mg / 5ml	200mg-400mg BID or Q 12 HOURS UNTIL GONE.

MISCELLANEOUS

Clindamycin (Cleocin, generic)	***Capsules:***75mg,150mg,300mg	150-450mg QID OR Q 6 HOURS UNTIL GONE.
Metronidazole (Flagyl,generic)	**Capsules**: 375mg **Tablets**: 250mg, 500mg	1-2 GRAMS DAILY AS: 250MG QID OR 375MG TID OR 500MG TID – QID.

MACROLIDES

Name	Usual Dosages	Usual Regimens
Clarithromycin (Biaxin, generic)	**Oral Powder for Suspension**: 125 MG/5 ML, 250 MG/5 ML **Oral Tablet**: 250 MG, 500 MG **Oral Tablet**, Extended Release: 500 MG	250mg-500mg BID OR Q 12 HOURS UNTIL GONE.
Azithromycin (Zithromax Z-Pak)	**Oral Powder for Suspension:** 1 GM/Packet, 100 MG/5 ML, 200 MG/5 ML **Oral Tablet**: 250 MG, 500 MG, 600 MG	500mg on Day 1, followed by 250mg daily for 4 more days.

FLUOROQUINOLONES

Name	Usual Dosages	Usual Regimens
Levofloxacin (Levaquin,generic)	Oral Tablet: 250 MG, 500 MG, 750 MG	250mg-500mg QD UNTIL GONE
Moxifloxacin (Avelox)	Oral Tablet: 400mg	400mg QD UNTIL GONE

Clinical features of odontogenic orofacial and peripharyngeal "space" infections

Space infections	Usual site of origin	Clinical features				
		Pain	Trismus	Swelling	Dysphagia	Dyspnea
Masticator						
Masseteric and pterygoid	Molars (especially 3rd)	+	+++	May not be evident (deep)	-	-
Temporal	Post. maxillary molars	+	-	Face, orbit (late)	-	-
Buccal	Bicuspids, molars	±	±	Cheek (marked)	-	-
Canine	Maxillary canines, incisors	++	-	Upper lip, canine fossa	-	-
Infratemporal	Post. maxillary molars	+	-	Face, orbit (late)	±	±
Submental parotid	Mandibular incisors	++	-	Chin (firm)	-	-
Submandibular	Masseteric spaces	+++	-	Angle of jaw (marked)	-	-
Sublingual	2nd, 3rd mandibular molars	+	±	Submandibular (brawny)	-	-
Lateral pharyngeal						
Anterior	Mandibular incisors	+	±	Floor of mouth (tender)	+ (if bilateral)	+ (if bilateral)
Posterior	Masticator spaces	+++	+++	Angle of jaw	+	±
Retropharyngeal (and "danger")	Masticator spaces	±	±	Post. pharynx	+	+++
	Lateral pharyngeal space, distant via lymphatics	+	±	Post. pharynx (midline)	+	+
Pretracheal	Retropharyngeal space, anterior esophagus	+	-	Hypopharynx	+	+++

±: minimal or occasional; +: present; ++: moderate; +++: prominent or severe.

CONTROVERSIAL ISSUES IN ANTIBIOTIC PROPHYLAXIS

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I. ANTIMICROBIAL PROPHYLAXIS: PRINCIPLES & PRACTICE

A. RISK FACTORS FOR POST-OPERATIVE INFECTIONS:

1. Proportional to the degree of bacterial contamination during surgery – dirty vs. clean surgeries
2. Virulence of the infective organism – HA-MRSA or CA-MRSA?
3. Host factors – immunocompromised?

B. TIMING OF SURGICAL PROPHYLAXIS

IV REGIMENS: Recommend a single dose given just prior to surgery
Give follow-up dose when: drug has short $t_{1/2}$, for prolonged surgeries, ↑ blood loss
PO REGIMENS: Peak plasma concentration of antibiotic should occur when surgery begins

C. SOURCES OF BACTERIAL CONTAMINATION

EXOGENOUS: Due to poor aseptic technique, high O.R. traffic, colonized surgeons

ENDOGENOUS: Flora from patient's skin, GI, GU, or respiratory tract, dirty wounds (pus)
most common cause of post-op infections

D. ANTIMICROBIAL AGENTS

MECHANISM OF ACTION ??: ↓ Level of bacteremia and bacterial growth after adherence
Prevents adherence of bacteria to defect or prosthetic device

- Direct prophylaxis against the <u>most likely</u> infective organisms:
  - Usually normal skin flora
  - Target specific organisms

- For dental procedures: Coverage of Viridans streptococci
  - Amoxicillin preferred by A.H.A. (American Heart Association) over penicillin VK citing better absorption & more prolonged serum levels

F. HEALTH QUESTIONNAIRE IDENTIFIERS

Possible Risk from Oral Bacteremia:

YES NO ? a. Artificial heart valve replacement
YES NO ? b. History of bacterial endocarditis
YES NO ? c. Congenital heart disease (type _____)
YES NO ? d. Acquired valvular heart disease or heart murmur (no longer necessary to ask)
YES NO ? e. History of post-streptococcal glomerulonephritis
YES NO ? f. Organ transplantation
YES NO ? g. Prosthetic joint replacement (when_____)
YES NO ? h. Artificial implant or graft of any kind other than above (list _____)
YES NO ? i. Systemic lupus erythematosus (SLE)
YES NO ? j. Immunosuppression? Asplenic?
YES NO ? k. Physician requests antibiotic coverage for reasons other than above (reason_____)

II. ANTIBIOTIC PROPHYLAXIS FOR PATIENTS WITH TOTAL JOINT REPLACEMENTS

A. GUIDELINES FOR ANTIMICROBIAL PROPHYLAXIS – TIMELINE FROM 2003 THROUGH 2015

- Advisory statement adopted by the ADA and the AAOS (American Academy of Orthopedic Surgeons), published JADA 134:895-899, July 2003. AAOS "retired" that advisory statement in February of 2009.
- February 2009 AAOS Information Statement recommends lifelong antimicrobial prophylaxis for all patients with total replacements of large weight-bearing joints even though no new evidence for the change exists.
- *Given this new "Information Statement", Orthopedic Surgeons now bear prescriptive responsibility if the dentist does not deem premedication to be appropriate. See* ***Clinical Infectious Diseases****,1/1/10 and* **JADA***;141;667-671. (Position Paper from the AAOM on Dental Treatment of Joint Patients);Also see JADA December 2011.*
- **Evidence-based recommendation issued December 18, 2012 with guideline writing committee appointed.**

This clinical practice guideline, with three recommendations, is based on a systematic review of the correlation between dental procedures and prosthetic joint infection (PJI).
• Recommendation one, which is based on limited evidence, supports that practitioners consider changing their longstanding practice of prescribing prophylactic antibiotics for patients who undergo dental procedures. Limited evidence shows that dental procedures are unrelated to PJI.
• Recommendation two addresses the use of oral topical antimicrobials (topical antibiotic administered by a dentist) in the prevention of PJI in patients undergoing dental procedures. There is no direct evidence that the use of oral topical antimicrobials before dental procedures will prevent PJI.
• Recommendation three is the only consensus recommendation in the guideline, and it supports the maintenance of good oral hygiene.

B. ADA Constitutes 2014 Committee and Publishes Clinical Recommendations in January 2015

Management of patients with prosthetic joints undergoing dental procedures

Clinical Recommendation:
In general, for patients with prosthetic joint implants, prophylactic antibiotics are *not* recommended prior to dental procedures to prevent prosthetic joint infection.

For patients with a history of complications associated with their joint replacement surgery who are undergoing dental procedures that include gingival manipulation or mucosal incision, prophylactic antibiotics should only be considered after consultation with the patient and orthopedic surgeon.* To assess a patient's medical status, a complete health history is always recommended when making final decisions regarding the need for antibiotic prophylaxis.

Clinical Reasoning for the Recommendation:

- There is evidence that dental procedures are not associated with prosthetic joint implant infections.
- There is evidence that antibiotics provided before oral care do not prevent prosthetic joint implant infections.
- There are potential harms of antibiotics including risk for anaphylaxis, antibiotic resistance, and opportunistic infections like *Clostridium difficile.*
- The benefits of antibiotic prophylaxis may not exceed the harms for most patients.
- The individual patient's circumstances and preferences should be considered when deciding whether to prescribe prophylactic antibiotics prior to dental procedures.

ADA. Center for Evidence-Based Dentistry™

* In cases where antibiotics are deemed necessary, it is most appropriate that the orthopedic surgeon recommend the appropriate antibiotic regimen and when reasonable write the prescription.

C. Shared Decision-Making Tool is Advocated By Some Organizations and Institutions

Decision Making Guide:
Should I take antibiotics before my dental procedure?

This shared decision making tool was developed by a special workgroup involving the American Academy of Orthopaedic Surgeons and the American Dental Association. This guide will assist patients who have had a joint replacement in deciding, with their doctor and dentist, whether they should take antibiotics prior to any dental procedure. This guide will help to clarify the risks, benefits and alternatives involved in making this decision.

Your Implant and Infection

If you have an orthopaedic implant (such as a joint replacement, metal plates or rods), please understand:

- A potential complication of these implants is bacterial infection, which occurs in approximately 1-3% of patients. These infections require more surgery as well as antibiotic usage for an extended period of time. Most infections occur around the time of the procedure (within one year after your surgery), but some have occurred much later.
- In theory, infections that happen long after your surgery (beyond one year post-operatively) are caused by the spread of bacteria from the bloodstream to the implant. Unfortunately, there is no clear scientific evidence to support this theory. We know that many patients with orthopaedic implants frequently have bacteria in their blood that do not spread to their implants.

Infections and dental procedures

Dental procedures have long been considered a potential cause of implant infections, even after the initial orthopaedic post-operative period. The reason for this is that dental procedures can introduce bacteria from the mouth into the bloodstream. Please keep in mind, however, that eating and performing regular oral hygiene at home may also introduce oral bacteria into the blood. Here are important points to consider:

- Traditionally, antibiotics have been provided prior to dental procedures in patients with orthopaedic implants to minimize the bacteria that get into the blood.
- The best evidence we have currently, however, does not show that antibiotics provided before oral care can help to prevent infections of orthopaedic implants.
- The routine use of antibiotics in this manner has potential side-effects such as increased bacterial resistance, allergic reactions, diarrhea, and may even cause death.

Patients with compromised immune systems

Patients who have compromised immune systems might be at greater risk for implant infections. Medical professionals recommend that patients with diabetes, rheumatoid arthritis, cancer, those receiving chemotherapy or those using steroids on a regular basis should take antibiotics prior to dental procedures. Please discuss your situation with your physician or dentist.

Decision Making Guide:
Should I take antibiotics before my dental procedure?

Test questions

Patients with orthopaedic implants have what chance of infection?:

a. 0% chance
b. 0-1% chance
c. 1-3% chance
d. >3% chance

Most implant infections:

a. Are related to dental procedures
b. Occur around the time of surgery
c. Are related to skin infections
d. Occur long after surgery

Some dental procedures:

a. Routinely cause implant infections
b. Are the primary source of implant infections
c. Never cause implant infections
d. Allow bacteria to enter the bloodstream

Routine pre-dental procedure antibiotics:

a. Are not supported by current evidence
b. May be beneficial to certain groups of patients
c. Are associated with other unwanted side effects
d. All of the above

Patient checklist

1. I have adequate understanding of implant infections associated with dental procedures:
   [ ] YES [ ] NO
2. My physician or dentist has discussed my specific risk factors with me:
   [ ] YES [ ] NO
3. I need further education and discussion on this issue:
   [ ] YES [ ] NO
4. I am immune-compromised because I have:
   _____
   _____
5. Based on this educational material and discussion with my physician or dentist:
   [ ] I will not take antibiotics before my dental procedures.
   [ ] I will take antibiotics before my dental procedures.

D. PATIENTS AT INCREASED RISK OF LATE INFECTION

IMMUNOCOMPROMISED – IMMUNOSUPPRESSED

- Disease: diabetics with HgA1c of 8 or more, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), other collagen vascular disorders
- Drugs: glucocorticoids , immunomodulators or antineoplastics
- Treatment: radiation therapy

OTHER PATIENTS AT INCREASED RISK

- Patients with chronic infections: e.g. urinary or respiratory tract infections, chronic periodontitis
- Malnourished or Hemophiliac

ORTHOPEDIC RISK

- Patients with history of post placement complications – previous infection in joint, recent dislocation, recent capillary hemorrhage near prosthesis, re-operated joints, etc.
- Joint in place less than 2 years

E. SCREENING QUESTIONS FOR PATIENTS

YES NO ? DO YOU HAVE ANY ARTIFICIAL JOINTS? (if yes, answer questions below)

1. How long have you had the prosthetic joint? (date of surgery _____)
   (note: if 2 yrs. or less = premedicate, if greater than 2 years = no need for premedication unless "yes" to questions 2 and/or 3)
2. YES…NO…? Have you had any problems with the joint since it was replaced?
3. YES…NO…? Is your immune system suppressed by disease, medications or treatments?

F. PRESCRIPTIONS

Rx: Amoxicillin 500 mg capsules
or
Cephalexin 500 mg capsules
Disp: # 4
Sig: Take 4 capsules p.o. 1 hr. prior to dental appointment

- **Amox Is for patients NOT allergic to penicillin**
- Cephalexin is a 1st generation cephalosporin with good strep. coverage and active against staphylococcal organisms

Rx: Clindamycin 150 mg capsules
Disp: # 4
Sig: Take 4 capsules p.o. 1 hr. prior to dental appointment

- For patients with penicillin allergy
- 150 mg capsules available generically

Rx: Cefazolin 1 gram **or** Ampicillin 1 gram
Administer: I.M. or I.V.
Sig: 1 hr. prior to procedure

- For patients unable to take oral medications AND NOT allergic to penicillin

Rx: Clindamycin 600 mg
Administer: I.V.
Sig: 1 hr. prior to procedure

- For patients unable to take oral medications AND penicillin allergic

G. DENTAL MANAGEMENT OF PATIENTS WITH TOTAL JOINT REPLACEMENTS

- Updated health history with each visit and explain why you ask at every visit
- Reinforce home-care procedures and use chemotherapeutic measures to reduce bleeding
- Immediate and aggressive treatment of acute and newly recognized chronic infections
- Avoidance of regular daily bacteremia

III. PROPHYLAXIS FOR OTHER IMPLANTS AND DEVICES

A. NO PROPHYLAXIS NECESSARY:

- Breast implants
- **Intraocular lenses**
- Dental implants
- Cochlear implants
- Cardiac Pacemakers
- **A.I.C.D. (Artificially Implanted Cardiac Defibrillators)**
- Orthopedic Plates, Pins, Screws, and Wires
- Hernia Repair Mesh, Vascular Screens

B. PENILE PROSTHESES

BACKGROUND: 30% of men over 40 yrs. have erectile problems due to:
- arteriosclerotic disease, endocrine problems
- medications (25%) e.g. antihypertensives, diuretics alcohol, tobacco

MANAGEMENT: Defer elective dental treatment until 3 months post-op
ANTIBIOTIC *PROPHYLAXIS?? Not unless immunosuppressant co-morbidities are present*

C. VASCULAR GRAFTS

BACKGROUND: 1 – 5 % incidence of infections
- varies with the site of graft placements
- organisms often originate from bowel or skin

MANAGEMENT: Antibiotic prophylaxis is indicated for grafts < 6 months old
- pseudointima (connective tissue & fibrin) forms on the inner surface of the graft
- physician consult to determine size, type and location of graft

D. INTRAVASCULAR ACCESS DEVICES

BACKGROUND:

Central (tunnel) I.V. lines

- Broviac or Hickman lines - for chemotherapy
- Uldall catheters - for hemodialysis, plasmaphoresis

- Infections primarily due to skin contamination
- Increased risk with newer grafts

MANAGEMENT: No invasive procedures within 6 weeks of graft placement or revision

- Hemodialysis patients (JADA. Dental Considerations for the Patient with Renal Disease. 127:211-19, 1996)
  - at ⇧ risk of S.B.E., Viridans group Strep is responsible for 17% of I.E. cases in renal failure patients
  - ? mechanism – long term cardiac valve problems with hemodialysis patients
  - consult hemodialysis clinic for their recommendation-some still use AHA recommendations
  - **home maintenance of oral hygiene is crucial to avoid shunt infection**

E. CEREBROSPINAL FLUID SHUNTS

- **Ventricluoatrial shunts (ventriculoatriostomy)– at risk, premedicate**
  - old procedure where tube from brain ventricle empties into heart atrium

- Lumboperitoneal shunts – negligible risk, no prophylaxis needed

- Ventriculoperitoneal shunts – negligible risk, no prophylaxis needed
  - Most common procedure performed today
  - Used to treat hydrocephalus, post-stroke injury
  - Used to treat normal pressure hydrocephalus (NPH) which is a reversible cause of dementia

IV. PROPHYLAXIS FOR THE PREVENTION OF SUBACUTE BACTERIAL ENDOCARDITIS (SBE) – CIRCULATION, APRIL 19, 2007

2007 AHA Guidelines for the Prevention of Infective Endocarditis

A. Regimens for a Dental Procedure

Situation	Agent	Regimen – Single dose 30-60 minutes before procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Oral Allergic to penicillins or ampicillin	Cephalexin**† *OR* Clindamycin *OR* Azithromycin *or* clarithromycin	2 g 600 mg 500 mg	50 m/kg 20 mg/kg 15 mg/kg
Unable to take oral medication	Ampicillin *OR* Cefazolin or ceftriaxone	2 g IM or IV* 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone† *OR* Clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

*IM – intramuscular; IV – intravenous.
**or other first or second generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin

B. Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis For Which Prophylaxis with Dental Procedures Is Recommended (Table 3.)

Prosthetic cardiac valve

Previous infective endocarditis

Congenital heart disease (CHD)*

- Unrepaired cyanotic CHD, including palliative shunts and conduits
- Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure**
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)

Cardiac transplantation recipients who develop cardiac valvulopathy

* Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form Of congenital heart disease (CHD).
**Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months After the procedure

C. Dental Procedures for which Endocarditis Prophylaxis is Recommended for Patients

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa *

***The following procedures and events do not need prophylaxis**: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa.

D. SAMPLE ADULT ANTIBIOTIC PREMEDICATION PRESCRIPTIONS

RX: Amoxicillin 500 mg capsules
Disp. # 4
Sig: Take 4 capsules p.o. 1 hour before dental Appointment

- **For patients NOT penicillin allergic**
- Pediatric dose: 50 mg/kg not to exceed adult dose!
- Amoxicillin is available in 500 and 250 mg **capsules**, and 250 mg chewable tablets and 250 mg/5 ml susp.
- Amoxicillin ≠ ampicillin ≠ penicillin VK

RX: Clindamycin 150 mg capsules
Disp. # 4
Sig: Take 4 capsules (600 mg) p.o. 1 hour before dental appointment. Take with food or milk.

- **For patients with penicillin allergy**
- Pediatric dose: 20 mg/kg
- Clindamycin is a lincomycin, therefore not cross-reactive with the erythromycin family

RX: Cephalexin 500 mg capsules
OR
Cephradine 500 mg capsules
Disp. # 4
Sig: Take 4 capsules p.o. 1 hour before dental appointment

- Pediatric dose: 50 mg/kg
- Cephalexin (generic Keflex®) is less expensive than cephradine (generic Velosef® or Anspor®)
- Also comes in a 250 mg/5ml suspension
- Avoid cephalosporins if patients allergic reaction was either – urticarial, angioedema, anaphylaxis or unknown

RX: Clarithromycin (Biaxin®) 500 mg tablets
Disp. # 1
Sig: Take one tablet p.o. 1 hour before dental appointment.

- Pediatric dose: 15 mg/kg
- An erythromycin with low GI irritation

RX: Azithromycin (Zithromax®) 250 mg tablets
Disp. #2
Sig: Take 2 tablets p.o. 1 hour before dental appointment.

- Pediatric dose: 15 mg/kg
- Less drug interactions than macrolides, low incidence of GI irritation
- Very expensive, no therapeutic advantage over Biaxin© or EES

Oral liquids for adults who have forgotten to take premedication at home:

RX: Amoxicillin 250 mg/5 ml suspension
Disp. # 40 ml
Sig: Take 40 ml one-half to one hour before dental appointment

- Suspension is a powder that must be reconstituted prior to use- tastes good
- Reconstituted suspension expires in 14 days with or without refrigeration

RX: Erythromycin ethylsuccinate 400 mg/5 ml susp.
Disp. # 20 ml
Sig: Take 20 ml one-half hour before dental appointment

- Suspension is commercially available premixed
- Must be refrigerated, has a shelf life of about 2 years.
- Suspension is better tolerated (GI) than tablets

RX: Cleocin© 75 mg/5 ml solution
Disp. # 40 ml
Sig: Take 40 ml one-half hour before dental appointment

- Solution must be reconstituted & expires in 14 days
- Do NOT refrigerate
- Taste and smell are less than desirable

V. OTHER CONDITIONS THAT MAY REQUIRE ANTIMICROBIAL PROPHYLAXIS

A. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

BACKGROUND:

- SLE is an inflammatory autoimmune disease whereby pathogenic antigen-antibody complexes harm a variety of organs & systems including the skin, kidneys, blood vessels, joints and the heart
- 50% of SLE patients demonstrate cardiac valve abnormalities at autopsy
- SLE patients have an increased prevalence of cardiovascular abnormalities
- **Incidence of *Infective Endocarditis***: SLE = 1 - 7%
  RHD = 0.8 - 1.2%
  Prosthetic heart valve = 1.1%

MANAGEMENT: Progressive SLE patients should be regularly evaluated for the detection of new heart murmurs

And should be questioned about cardiac valve disease at dental visits.

B. ASPLENIC PATIENTS

BACKGROUND (JADA: Dental Considerations in Asplenic Patients. 127:1359-1363, 1996)

- Patients who are functionally or anatomically asplenic fail to clear organisms from the bloodstream and are at an increased risk of overwhelming bacteremia
- Reasons for splenectomy
- Encapsulated organisms pose the highest risk - primary pathogens of concern are *S. pneumoniae, H. influenzae, N. meningitidis, β-* hemolytic streptococci
- Splenectomy confers life-long risk from sepsis in both adults and children (2 - 4%)
- Recommend dental prophylaxis with current AHA regimen when needed

C. SOLID ORGAN TRANSPLANTATION

BACKGROUND: (Clin Transplant. A Survey of Dental Care Protocols. 19: 15-18, 2005)

- Infectious Disease Rates of Patients
  - 80% have "normal" rate of infections
  - 10% chronic or progressive viral infections
  - Hepatitis B or C, cytomegalovirus, EPV etc.
- Theoretically at ⇑ risk from transient bacteremias
- 5-10% recurrent or chronic rejection
  - Increased immunosuppressive dosages (tacrolimus,mycophenolate, prednisone)
  - Most likely to develop opportunistic infections

MANAGEMENT:

- Defer elective dental treatment until at least 6 months after transplantation

D. CORONARY ARTERY STENTS

BACKGROUND:

Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: A science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians
JADA May 2007 138(5): 652-655

The report published in *JADA* can be summarized for the dental professional as follows:

1. Dental professionals and other healthcare providers who perform invasive or surgical procedures and are concerned about periprocedural and postoperative bleeding must be made aware of the potential catastrophic risks of premature discontinuation of antiplatelet (thienopyridine) therapy. The dental professional should contact the patient's physician if issues regarding the patient's antiplatelet therapy are unclear, in order to discuss optimal patient management strategy.

2. Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of thienopyridine therapy. The course of this therapy is suggested as 12 months after drug-eluting stent implantation if they are not at high-risk of bleeding.

WHAT ABOUT ANTIBIOTIC PREMEDICATION??

* **According to the 2007 AHA SBE Prophylaxis guidelines, antibiotic prophylaxis is not indicated as stated in the last section called "other considerations".**

Anxiety Management in the Dental Office

I. Definition of Levels of Sedation and Analgesia by American Society of Anesthesiologists

	Minimal Sedation (Anxiolysis)	Moderate Sedation/Analgesia (Conscious Sedation)	Deep Sedation/Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response after repeated or painful stimulation	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

II. CHARACTERISTICS OF SPECIFIC AGENTS FOR DENTAL OFFICE USE

A. Antihistamines

1)Diphenhydramine (Benadryl)
Uses: histamine blocker (H_1); allergic reaction
Dose: (IV) 250 mg; (PO) 25-50 mg; pediatric 2-5mg/kg
Clearance: hepatic
Interaction/toxicity; MAOI's intensify effects;
May antagonize heparin; Avoid in seizure disorders;
Most drying of the 3 antihistamines

2)Hydroxyzine (Atarax, Vistaril)
Uses: sedative, antiemetic, analgesic adjunct
Dose: 25-100mg (IM) or (PO); pediatric 0.5-2.5 mg/kg
Clearance: hepatic
Interaction/toxicity; unsafe in porphyric patients;
reduce CNS depressant dose by 50% if given concomitantly

3)Promethazine (Phenergan)
Uses: sedative, antiemetic, analgesic adjunct
Dose: 12.5-25mg (IM); pediatric- 1mg/kg
Clearance: hepatic
Interaction/toxicity; hypersensitivity reaction
May manifest as jaundice.

B. Benzodiazepines

BENZODIAZEPINES OF USE IN ADULT SEDATIVE PREMEDICATION

DRUG	SEDATIVE DOSE RANGE	SPEED OF ONSET	PEAK LEVEL (HRS)	HALF-LIFE OF ELIMIN. T 1/2 (HRS)	ACTIVE METAB	AVAILABLE ORAL DOSAGE FORMS
diazepam (Valium,g)	5 - 20mg	very fast	0.5 - 2	20 - 80	YES	2, 5, 10mg tabs 5mg/5ml & **5mg/ml** oral solution (**Intensol-Roxane**)
lorazepam (Ativan, g)	1 - 5mg	intermediate	1 - 6	10 - 20	NO	0.5, 1, 2mg tabs
midazolam (Versed,g)	7.5 - 15 mg by mouth	fast	0.5	1.75	NO	1mg/ml & 5mg/ml injection 2mg/ml cherry syrup for oral use
oxazepam (Serax,g)	10 - 30mg	intermediate/ slow	2 - 4	5 - 20	NO	10, 15, 30mg caps
temazepam (Restoril,g)	15 - 30mg	intermediate/ slow	1 - 4	5 - 10	YES	7.5, 15, 30mg caps
triazolam (Halcion, g)	0.125 - .5mg	Intermediate	1.3	1.5 - 5	No	0.125, 0.25mg tabs

BENZODIAZEPINES FOR INTRAVENOUS SEDATION

	DIAZEPAM	MIDAZOLAM	LORAZEPAM
Anterograde amnesia	+	++	+
Retrograde amnesia	+	-	+
Rebound	+	-	?
Vein irritation	+	-	+
Administration rate	5mg/min.	1mg/ 2 min.	2mg/min.
Length of sedation	45 - 60 min.	45- 60 min.	6 - 8 hours

DIAZEPAM

1. AVAILABLE: Valium (Roche), generics
   5mg/ml predrawn syringes, multidose vials (MDV), ampules
2. CHARACTERISTICS:

   a) time to peak: 1-2 min. after administration
   b). propylene glycol & Et0H vehicle
   - avoid small veins of wrist and dorsum of hand
   - Open up IV infusion for administration to minimize irritation
   - NO ADMIXTURES
   - advise patients of possible "warm sensation" upon infusion

   c). anterograde amnesia in 75% of patients - lasts 10-15 min. after injection
   d). rebound (2nd peak effect) - occurs after patient ingests lipid containing meal after surgery. Caution patient and escort
   e) >98% protein bound
   -elderly have decreased protein binding = higher sensitivity

3. COMPLICATIONS
   a) hypotension, apnea, bradycardia, cardiac or respiratory arrest - administration too rapidly
   b) venous irritation – extreme cases of extravasation caused by rapid administration
   c) recurrence of amnesia - dose > 30mg
   d) oversedation - maintain vital signs and wait for drug to redistribute
   e) intra-arterial injection - arteriospasm, gangrene

MIDAZOLAM

1. AVAILABLE: Versed (Roche, generics)
   1mg/ml and 5mg/ml* vials
   *dilute 1 ml of 5mg/ml Versed with 4 ml D5W, NS, LR to give a final concentration of 1mg/ml
   **double check vial before administration

2. CHARACTERISTICS:
   a) onset of sedation: 1.5 - 5 min.
   b) 2 - 4 times potency of diazepam, <sedation, >anterograde amnesia
   c) water soluble - can be admixed with some narcotic agonists and anticholinergics
   -physically compatible in syringe for at least 30 min.
   d) 94-97% protein bound to serum albumin

3. COMPLICATIONS:
   Respiratory depression

4. DRUG INTERACTIONS:
   Metabolism inhibited by erythromycin, ketoconazole, CCB, cimetidine, omeprazole
   -possible prolonged sedation

LORAZEPAM

1. AVAILABLE: Ativan (Wyeth), generics
2mg/ml and 4mg/ml predrawn syringes, tubex, MDV

2. CHARACTERISTICS

a) slow onset - can't titrate to effect
b) prolonged sedation 24 - 48 hours
c) exaggerated amnestic properties
d) water insoluble - admixed IMMEDIATELY prior to injection with equal volume of NS, 5% dextrose injection, sterile water for injection

CONTRAINDICATIONS TO BENZODIAZEPINES

- Allergy or hypersensitivity to benzodiazepines
- Untreated or unrecognized narrow angle glaucoma
- History of phlebitis or thrombophlebitis
- Acute pulmonary insufficiency (midazolam)
- Pre-existing respiratory depression

C. Other Oral Medications Used for Dental Office Anxiolysis

1) Characteristics of Oral Medications Useful for Office Dental Anxiolysis

Drug Name	Sedative Dose Range	Time to Peak Effect	Half-Life (in hours)	Comments
Eszopiclone (Lunesta,g)	2-3mg (3mg usual dose)	1.0 hours	6.0 hours	Hangover effect
Melatonin Sublingual	.3-6mg (5mg usual dose)	0.5-1.0 hours	0.5-2.0 hours	Must give sublingual
Ramelteon (Rozerem)	2-8mg (8mg usual dose)	1.0-1.5 hours	1.0-2.6 hours	Avoid high fat meal
Zaleplon (Sonata,g)	5-10mg(10mg usual dose	1.0 hours	1.0 hours	Little hangover,Preg C
Zolpidem (Ambien, G)	5-10mg(10mg usual dose	1.6 hours	2.6 hours	Pregnancy Category C

2) Clinical Use of Specific Agents

A. Zaleplon (Sonata) – most studied in clinical dentistry
-preservation of sleep architecture with less rebound insomnia
-low risk of tolerance and physical dependence

B. Zolpidem (Ambien, G) – cheapest of the prescription drugs listed above
-same characteristics as zaleplon

C. Melatonin Sublingual – over-the-counter supplement
-secretion of melatonin from the pineal gland decreases with age
-thought to be the most effective for older patients with decreased melatonin secretion
-no tolerance reported and no abuse potential seen with melatonin

D. Ramelteon (Rozerem) – is a melatonin receptor agonist with no abuse potential
-may increase serum prolactin levels in females
-too expensive to use regularly and no studies done for dental anxiety

D. Opioids

1) Chemical Classification of Opioids
   a. Phenanthrenes-morphine, codeine, oxycodone, hydrocodone, nalbuphine (Nubain), hydromorphone,tramadol?
   b. Phenylpiperidines-meperidine, fentanyl, alfentanil, sufentanil, remifentanil
   c. Phenylheptylamines- methadone
   d. Morphinams-butorphanol (Stadol, Stadol NS, g)
   e. Benzomorphans-pentazocine (Talwin Nx, g)

2) Relative Potency and Plasma Concentration Effects

Relative Potencies and Plasma Concentrations for Various Opioid Effects

Effect	Morphine	Meperidine	Fentanyl	Sufentanil	Alfentanil	Remifentar
Relative potencies	1	0.1	100	500-1000	10-20	-
Analgesic dose (mg)	10	100	0.1	0.01-0.02	0.5-1.5	-
Minimum effective analgesic concentration (ng/ml)	10-15	200	0.6	0.03	15	-
Moderate to strong analgesia (ng/ml)	20-50	400-600	1.5-5.1	0.05-0.11	40-80	-
Decrease MAC 50% (ng/ml)	NA	>500	0.5-2	0.145	200	1.3
Surgical analgesia with 70% nitrous oxide (ng/ml)	NA	NA	15-25	NA	300-500	-
Depression of ventilation threshold (ng/ml)	25	200	1	0.02-0.04	50-100	-
Ventilatory response to carbon dioxide decreased 50% (ng/ml)	50	NA	1.5-3	0.04	120-350	2.1-2.9
Apnea (ng/ml)	NA	NA	7-22	NA	300-600	-
Unconsciousness (not reliably achieved with opioids alone) (ng/ml)		Seizures	15-20	NA	500-1500	-

*RECOMMENDED DOSAGES FOR PEDIATRIC SEDATION AND ANALGESIA**

DRUG	DOSE	TIME TO ONSET (min.)	DURATION OF ACTION (min.)
Antihistamines			
Diphenhydramne	IM: 1.25mg/kg	20-30	60-120
	PO: 2-5mg/kg	15-60	60-120
Hydroxyzine	IM: 1mg/kg	20-30	60-120
	PO: 0.5-2.5mg/kg	30-60	60-120
Promethazine	IM: 0.5-1mg/kg	20-30	60-120
	PO: 0.5-1mg/kg	15-60	60-120
Sedative-hypnotic agents			
Choral Hydrate	PO: 25-100 mg/kg; after 30 min. may repeat 25-50mg/kg. Max does: 2 g or 100 mg/kg (whichever is less).	15-30	60-120
Midazolam	IV(0.5-5yrs): initially 0.05-0.1mg/kg, then adjusted to a max. of 0.6mg/kg	2-3	45-60
	IV (6-12 yrs): initially 0.025-0.05mg/kg, then adjusted to a max. of 0.4mg/kg		
	IM: 0.1-0.15mg/kg	10-20	60-120
	PO: 0.2-0.75 mg/kg (usual dose is 0.5mg/kg)	15-30	60-90
	IN: 0.2-0.5mg/kg	10-15	60
	PR: 0.25-0.5mg/kg	10-30	60-90
Pentobarbatal	IV: 1-6mg/kg, adjusted in increments of 1-2mg/kg	3-5	15-45
	IM: 2-6mg/kg, to a max. of 100mg	10-15	60-120
	PO or PR (<4yrs): 3-6mg/kg, to a max of 100mg	15-60	60-240
	PO or PR (≥ 4yrs): 1.5-3mg.kg, to a max of 100mg		
Methohexital	PR: 25mg/kg	10-15	60
Thiopental	PR: 25mg/kg	10-15	60-120
Analgesic Agents			
Fentanyl	IV: 1.0 mcg/kg/dose, may repeat every 3 min.	2-3	30-60
Ketamine	IV: 1-1.5mg/kg over 1-2 min., may repeat ½ dose every 10 min. as required	1	Dissociation: 15 Recovery: 60
	IM: 4-5mg/kg, may repeat after 10 min.	3-5	Dissociation: 15-30 Recovery: 90-150
Nitrous Oxide	Preset mixture with min. of 40% oxygen self-administered by demand-valve mask	<5	<5 after discontinuation
Reversal Agents			
Naloxone	IV/IM: 0.1mg/kg/dose, max 2mg/dose; may repeat every 2 min.	IV: 2 IM: 10-15	IV: 20-40 IM: 60-90
Flumazenil	IV: 0.02mg/kg/dose, may repeat every 1 min. to a max. of 1mg	1-2	30-60

*Alterations in dosing may be indicated based on individual patient situations and practitioner experience. Dosages must be adjusted when agents are combined, especially when benzodiazepines are combined with opioids.

Therapeutic Agents and Treatment Strategies for the Management of Selected Mucosal Diseases

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Footnote Key:

1. These medications are all contraindicated in microbial diseases. If given to patients with microbial diseases, microbial proliferation is usually enhanced and systemic dissemination is possible. Candidosis is a common side effect.

2. Systemic steroids are contraindicated or must be used with caution in a number of systemic conditions. Consultation with the patient's physician is recommended before prescribing. Tapering of prednisone is not necessary with 5-7 day burst therapy. Tapering of prednisone is not necessary with alternate day therapy (QOD) if the dosage does not exceed 20 mg QOD. In order to reduce the possibility of adrenocortical suppression, it is important that prednisone be taken in harmony with diurnal adrenocortical steroid levels. In order to accomplish this, prednisone should be taken 1-1/2 hours after normal arising time. Alternate day AM (QOD) dosage also reduces the possibility of adrenocortical suppression.

3. Whenever topical mouth rinses or ointments are prescribed, the manner in which the medication is used is very important. The patient should be advised that the medications are effective on contact and that they should avoid anything by mouth (NPO) for 1/2-1 hour after using them to prolong medication contact time.

4. Baseline hematology laboratory studies to include platelets are necessary to monitor possible bone marrow suppression.

5. Hepatotoxicity has been reported. **OPRM Faculty**

*** Denotes prescription items that must be extemporaneously compounded by a pharmacist.** Usually a specialty "compounding pharmacy" is a better choice as they have more experience and knowledge regarding product formulation.

Extemporaneously Compounding Medications for Intraoral Conditions

- Few products available in the U.S
- Limited product demand???
  - Problems - Difficulty with insurance payments, XIX & Medicare will not reimburse for the full cost of compounded prescriptions &"I can do that" - generalized lack of knowledge
  - Make sure products are not flavored or sweetened (especially with sucrose) unless necessary!

I. CHRONIC NON-MICROBIAL MUCOSITIS

(aphthous stomatitis, erosive lichen planus, mucous membrane pemphigoid, pemphigus, erythema multiforme)

Mouth rinses: Magic mouth rinse, Miracle mouth rinse, 1,2,3 Special mouth rinse formulas, etc.

DON'T bother!! WHY:

- *Nystatin 12,500 units/ml*
  - Normal nystatin 100,000/ml
  - 8 fold decrease from our minimum therapeutic agent
- *Benadryl 1.25 mg/ml*
  - 7.5 mg fairly low dose too
  - 25 mg much more commonly used
  - Does give a topical anesthetic effect at least in the higher concentrations
- *Hydrocortisone*
  - Hydrocortisone 0.25 mg/ml
  - 10 fold decrease from dexamethasone 0.5mg/5ml
  - 20 fold decrease from 0.1% triamcinolone acetonide suspension
- *Kaopectate®*
  - Many older formulas use the attapulgite clay in Kaopectate® to coat the mucosa. This product has been reformulated and now contains bismuth subsalicylate, which can cause a grayish-black discoloration of the tongue and is contraindicated in patients with hypersensitivity to salicylates.

Baseline initiatives to allow therapies to work:

- *Decrease common possible irritants – Avoid:*
  - Pyrophosphates
  - Cinnamon
  - Menthols, phenols, etc.
- *Maintain "salivary pellicle"*
  - Avoid sodium lauryl sulfate (SLS)
  - Avoid EtOH if possible
- *Maintain saliva*
  - Xerogenic agents
  - Hydration
- *Manage bugs*
  - Bacteria
  - Fungi

Mouth rinses[1,3]

***RX*:** **Dexamethasone 0.5 mg /5 ml oral solution**[1]
Disp: 240 ml
Sig: Rinse with 5 ml for 1 min. and expectorate QID, PC (after meals) and HS (before retiring). NPO 1\2 hr

- Commercial version
- Covered by Medicare Part D and HMOs in general
- Watch ethanol % in brands- Roxane brand is EtOH free
- Use correct strength to avoid toxicity

***RX**: **Triamcinolone acetonide (μ) 0.1 OR 0.2% aqueous suspension**[1]
Disp: 240 ml
Sig: Rinse with 5 ml for 1 min. and expectorate QID, PC (after meals) and HS (before retiring). NPO 1\2 hr.

- *About 2 x stronger than the commercial dexamethasone*
- Use the 0.2% for more severe cases
- 4 cc 95% EtOH per 240 ml
- Best if made with micronized powder (μ) vs. commercial injectable suspension (also much less expensive)

***RX**: **Triamcinolone acetonide (μ) 0.1 OR 0.2% in nystatin 100,000 U/ml suspension**
Disp: 240 ml
Sig: Rinse with 5 ml for 1 min. and expectorate QID, PC (after meals) and HS (before retiring). NPO 1\2 hr

- Use in patients predisposed to candidosis
- Commercial nystatin suspension is 30-50% sucrose
- We make a sugar-free nystatin suspension at the COD

***RX**: **Triamcinolone acetonide (μ) 0.1 OR 0.2% in amphotericin-B 15mg/ml suspension**
Disp: 240 ml
Sig: Rinse with 5 ml for 1 min. and expectorate QID, PC and HS. NPO 1\2 hr.

- Use in patients predisposed to candidosis
- Our amphotericin-B suspension is sugar-free
- More efficacious than nystatin suspension
- Use amphotericin-B 25 mg/ml if needed

Ointment [1, 3]

RX: **Triamcinolone acetonide 0.1% OR 0.5% ointment**
Disp: 15 gm
Sig: Apply thin film to inner surface of dentures or medication trays up to QID, NPO 1/2 hr.
- We usually use higher potency steroids in trays

- Low to medium potency steroid, price $18
- Use 0.1% strength on lips and dermis
- Still fluorinated and can thin lips or dermis long term Choose desonide instead for chronic use
- Seat trays for 30 min., then rinse mouth

RX: **Fluocinonide 0.05% OR clobetasol 0.05% ointment**
Disp: 15 gm
Sig: Apply thin film to inner surface of dentures or medication trays BID. Seat for 30 minutes

- Commercial products
- High potency steroids
- Instruct patients to expectorate & rinse mouth thoroughly after use
- Price of commercial products $100-190 for 15 g tube

Occlusive Ointment [1,3]

✱*RX:* **Triamcinolone acet. 0.5% ointment 1:1 with Orabase®**
Disp: 30 gm
Sig: Apply thin film to dried mucosa BID-QID, PC & HS Do not rub in. NPO 1/2 hr.

- Orabase® contains benzocaine. Allergenicity?
- Lower potency mixture due to 1:1 dilution
- Prescribe ointments to mix with Orabase® (never creams)
- Rubbing causes the Orabase® to become grainy & lose elasticity – RPh must mix ingredients very gently to avoid a grainy/ineffective product

✱*RX:* **Clobetasol .05 % ointment 1:1 with Orabase®**
Disp: 30 gm
Sig: Apply thin film to dried mucosa BID. Do not rub in. NPO 1/2 hr.

- Compounded clobetasol ointment mixed 1:1 with Orabase®
- Use higher concentrations of clobetasol ointment for recalcitrant lesions

RX: **Triamcinolone 0.1% in Orabase®**
Disp: 5 gm tube
Sig: Apply thin film to dried mucosa QID. Do not rub in. NPO 1/2 hr

- Commercially available but cost to patient approximately $80 per 5 gram tube!
- Low concentration of triamcinolone
- Good "bandage" effect, useful in pediatric patients

Combined Anti-inflammatory & Antimycotic Topical Agents [1]

✱*RX:* Clotrimazole 1% cream mixed **1:1 with triamcinolone acetonide 0.5% oint.**
Disp: 30 gm
Sig: Apply thin film inner surface of dentures or medication trays BID. Seat for 30 minutes.

- For patients prone to candidosis
- Dilution factor is a potential problem
- Most retail pharmacies will compound these "1:1" type of compounds, no clotrimazole oint. on market

In reality – no pharmacies are going to mix the clotrimazole oint b/c the insurance companies won't pay for it

✱*RX:* Clobetasol 0.03%, clotrimazole 2% ointment
Disp: 10, 20 or 40 gm
Sig: Apply thin film inner surface of dentures or medication trays BID. Seat for 30 minutes.

- Compounded from drug powders (not a 1:1 mixture)
- Allows for 2x commercial strength of clotrimazole
- Can customize strengths of both agents
- Ointment formulation is more occlusive than creams

Systemic and Intralesional Steroids

RX: **Prednisone 5 mg, 10 mg, 20 mg tabs[1,2]**
Disp: #
Sig: 40mg PO q A.M. (1-1/2 hrs after normal arising time) x 5 days followed by 10 mg QOD A.M. x 10 days

- Short bursts ≤ 3 weeks don't require taper
- Best taken with food

- Dose range 40-80 mg per day, depending on professional judgment; generally for severe acute cases such as erythema multiforme or initial therapy for long term unmanaged pemphigus, lichen planus or pemphigoid
- When daily dose is 30 mg or greater patients may experience insomnia, headache or irritability

RX: **Triamcinolone acetonide injectable 40 mg/ml (Kenalog®) diluted to 10 mg/ml or use Kenalog 10 mg/ml strength[1]**

- Best mixed with local anesthetic with epinephrine as the diluent
- Area should be anesthetized before injection of

Directions: Inject 10-40 mg (shake syringe immediately before use)

- Of value in management of solitary lesions recalcitrant to topical or systemic steroids

triamcinolone acetonide suspension if local anesthetic is not used.

II. BENIGN MUCOUS MEMBRANE PEMPHIGOID

Anticollagenase Agents

RX: **Doxycycline hyclate or minocycline 50-100 mg tabs/caps**
Disp: #30
Sig: Take QD or BID with food and plenty of water.

- Avoid taking HS – esophageal irritant
- Use as an adjunct to steroid therapy
- Avoid taking with antacids, iron, calcium tablets
- Nicotinamide has similar actions but requires close monitoring by a specialist
- Doxycycline $100, minocycline $50
- FDA pregnancy category: D

III. APHTHOUS STOMATITIS

Pathophysiology: Immunologic

- *Location: nonkeratinized, unattached mucosal surfaces*
  - Typically buccal vestibule, lateral or ventral tongue, floor of mouth
- *Heals in a predictable manner*
  - Types: minor, major, herpetiform
  - Treatment not usually necessary for the common minor type
- *Precipitating Factors:*

Cinnamon Oil	Genetics	Minor Oral Trauma
Medications	Stress	Dentifrices
Sodium Lauryl Sulfate (SLS)	Estrogen Shifts	

Primary Prevention Factors: Relate to maintenance of salivary pellicle or impeding the recognition of antigens to the immune system

Pharmacotherapeutic Management Choices:

- *Topical Route*
  - Treatment of choice: triamcinolone acetonide rinse - alters course of disease, increases healing rates
  - Steroid ointments, pastes
- *Systemic Route*
  - Prednisone - for difficult cases, large +/or multiple ulcerations
- *Over-The-Counter Products*
- *Inappropriate Chronic Treatment*
  - Cautery agents - do not affect course of disease (Debacterol®, silver nitrate, Negatan®, laser)
  - Tetracycline rinses, oral antibiotics etc.
- *Sodium Lauryl Sulfate (SLS) Free Dentifrices*

  Note: All SLS free products are not appropriate for some patients due to pyrophosphate content
  - Prevident® 5000+ Dry Mouth, 100 g container (only SLS free Prevident® product)
  - Biotène® (GSK) Fresh mint original (other Biotène®toothpaste is gentle mint – this formulation can be irritating)
  - Tom's of Maine Peppermint Clean and Gentle Fluoride Toothpaste
  - Sensodyne®: Original, Pronamels
  - Squigle Enamel Saver (with NaF) or Tooth Builder (with no fluoride and 40% xylitol)

IV. CANDIDIASIS

Topical Suspensions [3]

RX: **Nystatin oral suspension 100,000 U/ml**
Disp: 14 day supply (240 ml)
Sig: Rinse with 5 ml for 1 minute and expectorate P.C. (after meals) and HS (before retiring) NPO 1/2 hr.

- Commercial products contain 33-50% sucrose, not a first-line choice for this reason, especially in chronic/recurrent cases like Sjögrens, medicament xerostomia or post radiation xerostomia, $60/240 ml

***RX:** **Nystatin oral susp. 100,000 U/ml Sugar-Free**
Disp: 14 day supply (240 ml)
Sig: Rinse with 5 ml for 1 minute and expectorate P.C. (after meals) and HS (before retiring) NPO 1/2 hr.

- Viscous, will coat tissue
- Must be refrigerated, shorter shelf life than commercial, but not cariogenic

***RX:** **Amphotericin-B oral suspension 25mg/ml**
Disp: 14 day supply (280 ml)
Sig: Rinse with 5 ml for 1 minute and expectorate P.C. (after meals) and HS. (before retiring) NPO 1/2 hr.

- Much more effective than nystatin suspension
- Of use for fluconazole-refractory infections or when C. *krusei or* C. *glabrata* are suspected
- May use 15mg/ml strength when combining with triamcinolone acetonide

***RX:** **Clotrimazole 10 mg/ml gel**
Disp: 30 g
Sig: Swab thin film onto affected area QID, PC and HS, NPO 1/2 hr.

- Useful for debilitated patients who cannot rinse
- Compounded with clotrimazole powder and Biotène Oral Balance® Gel (GSK)

Ointment [3]

***RX:** **Nystatin ointment 100,000 U/g**
Disp: 15 gm
Sig: Apply thin film to inner surfaces of dentures and angles of mouth QID, PC & HS. NPO 1/2 hr.

- Inexpensive, but poor antifungal
- Works OK under dentures, but not first line agent
- Bright yellow color may be objectionable for angular cheilitis, $18

Cream [3]

***RX:** **Clotrimazole 1% cream (Rx, OTC as Lotrimin AF®, g)**
Disp: 15 gm Rx or 12 gm OTC
Sig: Apply thin film to inner surface of denture and angles of mouth QID. NPO 1/2 hr. after use.

- Has slight anti-staph activity
- Available OTC ($7) but labeled for athletes foot and jock itch which may cause some patients to hesitate. Identical product as Rx version ($18)

Lozenges and intraoral tablets [3]

***RX:** **Clotrimazole 10 mg oral troches**
Disp: 70 troches
Sig: Dissolve 1 troche in mouth every 3 hours while awake (5 tabs per day). NPO 1/2 hr. after use.

- Compliance problems with 5X daily therapy
- 1 troche QD HS or BID is useful for maintenance or prevention. $70-100
- FDA pregnancy category: C

Systemic [5]

***RX:** **Fluconazole 100 mg tablets**
Disp: #11-15 tabs
Sig: Take 1 tablet BID for first day, then take 1 tablet daily for 10 – 14 days.

- Cost of 15 tablets is approximately $50.00, cheaper to break 200 mg tablets in half
- Dose-related interactions with statin drugs, benzodiazepines, sulfonylureas, warfarin and some antihpertensives and many other drug classes – always check for interactions before prescribing
- FDA pregnancy category: D

Antibacterial Mouthrinse [3]

RX: **Chlorhexidine 0.12% oral rinse (Peridex®, g)**
Disp: 473 ml
Sig: 10 - 15 ml mouthrinse for 30 seconds and expectorate BID (after breakfast and HS, NPO 1\2 hr.

- 11.6% alcohol content will irritate ulcerations and enhance xerostomia, $13
- Due to chemical deactivation, separate from toothpaste by 30 min.
- FDA pregnancy category: B

RX: **Alcohol-Free Chlorhexidine 0.12% oral rinse (Paroex®)**
Disp: 473 ml
Sig: 10-15 ml mouthrinse 60-90 seconds and expectorate BID, PC, AM & HS. NPO 1/2 hr.

- Non-alcohol formulation – useful for alcoholics, patients with mucositis, xerostomia, $18
- Due to chemical deactivation, separate from toothpaste by 30 min.

V. HERPES & HERPES ZOSTER INFECTIONS

Herpes Labialis (Cold Sores, Fever Blisters)

- Virus remains dormant within the dorsal root ganglia until activated
- Asymptomatic viral shedding occurs for several days before the prodromal period & after lesions heal
- Specific triggers:
  - Sunlight (ultraviolet radiation) UVB
  - Tissue injury & inflammation
  - Physical or emotional stress: malnutrition, fever, colds, influenza, menstruation, exposure to extremes in temperature

Systemic Treatment of Herpes Labialis (Immunocompetent Patients)

RX: **Valacyclovir 1 g tablets (Valtrex®, g)**
Disp: 4 tablets
Sig: 2 tablets at onset of symptoms, then 2 tablets 12 hours after first dose

- Drug of choice -probably most efficacious therapy to date
- Price of 4 tablets $20
- A prodrug of acyclovir which is 3 times more bioavailable than acyclovir, may use in patients ≥ 12 years of age
- *WARNING:* Use with caution in renal & hepatic disease, has not been studied in pre-pubescent children
- Headache &/or nausea are dose related side effects (15%)
- FDA pregnancy category: B

RX: **Famciclovir 500 mg tablets (Famvir®, g)**
Disp: 3 tablets
Sig: Take 3 tablets (1500 mg) at onset of prodome

- Symptom duration decreased by 1.7 days when taken within an hour of onset of prodome
- Price of 3 tablets $30, not available in all pharmacies
- Best taken within 48 hours of symptom onset
- Can cause headaches, dizziness, GI upset
- Efficacy & safety haven't been established in patients under 18 years of age, adjust dosage in renal impairment
- 2nd line therapy after Valacyclovir
- FDA pregnancy category: B

Topical Treatment of Herpes Labialis (Immunocompetent patients)

- *Topicals are MUCH less efficacious than oral (systemic) therapy, prohibitively expensive and not recommended but included here for completeness. Note:* Topical creams and ointments are not appropriate for intraoral use

- We do not recommend topicals due to ineffectiveness and exteme expense of the Rx topicals

OTC: **Docosanol 10% cream (Abreva®)**
2 gm tube
Directions: Apply 5 times daily at onset of symptoms until lesions heal

- Recurrent HSV labialis studies (2) demonstrate mean duration of lesions & pain ↓ by ½ to 1 day
- ??? Efficacy compared to other topicals
- $20/2 g tube

RX: **Penciclovir 1% cream (Denavir®)**
Disp: 5 gm tube
Sig: Apply every 2 hrs during waking hours for 4 days beginning at the onset of symptoms

- Recurrent HSV labialis studies (2) demonstrate mean duration of lesions & pain ↓ by 1 day.
- More efficacious than acyclovir ointment
- Cost: >$815/5 g tube

RX: **Acyclovir 5% cream (Zovirax®) or ointment (Zovirax®,g)**
Disp: 5 gram tube cream (Zovirax®) 5 gram tube ointment
Sig: Apply thin film every 3 hrs (at least six times daily) at the onset of symptoms

- Little benefit, duration of Sx. decreased by ½ day
- 5 g tube of Zovirax cream $800, 5 g tube of generic oint. $140
- Recurrent HSV labialis shows no clinical benefit, but some ↓ in viral shedding
- Is NOT effective in prevention of recurrent herpes labialis

Systemic Agents for Primary & Recurrent HSV Gingiviostomatitis (Immunocompetent Patients)

- Acute herpetic gingivostomatitis can occur on both movable and attached oral mucosa. Recurrent infections in healthy patients are usually limited to attached gingival and hard palate
- *It is important to note that the duration of treatment for a primary case of HSV gingivostomatitis vs a recurrent case is different. Recurrent cases require shorter durations of treatment!!!*
- Short term therapy is indicated for patients who get recurrent herpetic after prolonged sun exposure, dental treatment, etc. Therapy must be initiated before exposure to any triggers. Start the day before trigger exposure and continue for a full course of treatment as listed below.

RX: **Valacyclovir 500 mg or 1 g (Valtrex®, g) caplet**
Primary HSV Gingivostomatitis :
Sig: 1 gram BID x *7-10 days*
Recurrent HSV Gingivostomatitis:
Sig: 500mg BID x *3 days* **Or** 1 g once daily x *5 days*

- *WARNING:* Use with caution in renal & hepatic disease, has not been studied in pre-pubescent children
- Headache & nausea are dose related side effects (15%)

RX: **Famciclovir 250 mg or 500 mg tablets**
Primary Gingivostomatitis HSV:
Sig: 250 mg TID x *7-10 days*
Recurrent Gingivostomatitis HSV:
Sig: 1000 mg BID x *1 day* **Or** 125 mg BID x 5 days

- Can cause headaches, dizziness, GI upset
- Best taken within 48 hours of symptom onset
- Efficacy & safety haven't been established in patients under 18 years of age

RX: **Acyclovir 400 mg (Zovirax®, g) tablet**
Primary HSV Gingivostomatitis:
Sig: 400 mg 3 times daily for *7-10 days*
Recurrent HSV Gingivostomatitis:
Sig: 400 mg 3 times daily for *5 days*
Or 800mg 3 times daily for *2 days*

- Only effective if initiated very early in recurrence
- *WARNING:* Use with caution in renal function impairment, dehydration
- FDA pregnancy category B
- Primary gingivostomatitis in children: Acyclovir 15 mg/kg PO 5 times daily for seven days (maximum of 1000 mg/day)

Prophylaxis for Recurrent HSV Infections (Immunocompetent Patients)

Prophylaxis for recurrent herpes labialis (RHL) and gingivostomatitis using oral antivirals:

- Long term prophylaxis is indicated if patients have at least six or more herpetic outbreaks per year. Reassess need every 6 – 12 months.

RX: **Acyclovir 400 mg (Zovirax®, generic)**
Disp: 60 tablets
Sig: Take 400 mg BID

- Must be given in divided doses
- Prophylactic doses between 800-1600 mg/day reduces the frequency of herpes labialis by 50 – 78%

RX: **Valacyclovir 500 mg (Valtrex®, generic)**
Disp: 30 caplets
Sig: Take 500 mg daily

- Doesn't appear to have large advantage over acyclovir
- Regimen for patients with >9 episodes/year is 1 gram QD

RX: **Famciclovir 500 mg (Famvir®, generic)**
Disp: 30 tablets
Sig: Take 500 mg BID

- No evidence that Famciclovir prevents RHL

Varicella Zoster Virus (VZV) Infections

- 25-fold decrease in zoster after immunization
- Patients with prior varicella zoster virus infection have a 20% chance of acquiring shingles

Trials showing benefit of Rx therapy only in patients treated within 3 days of onset of rash:

RX: **Valacyclovir 1 gram (Valtrex®, generic)**
Disp: 21 caplets
Sig: Take 1 caplet TID for *7 days*

- Drug of choice
- Patients should begin treatment within 72 hours of the onset of symptoms.
- More effective than acyclovir for cessation and duration of post-herpetic neuralgia
- *WARNING:* Use with caution in renal & hepatic disease

RX: **Famciclovir 500 mg (Famvir®, generic)**
Disp: 21 tablets
Sig: Take 1 tablet every 8 hours for *7 days*

- Prodrug of penciclovir, approximately same efficacy and safety as acyclovir
- Patients should begin treatment within 48 hours of onset of symptoms, efficacy after 72 hours is questionable
- *WARNING:* Use with caution in renal function impairment, has not been studied in children <18 years of age
- Equivalent to acyclovir in the duration of acute pain

RX: **Acyclovir 800 mg (Zovirax®, generic)**
Disp: 35 - 50 tablets
Sig: Take 1 tablet q 3 hours while awake (5 tablets per day) for *7-10 days*

- Therapy is most effective if started within 48 hrs after the onset of symptoms
- In our experience, oral acyclovir has been of value in controlling the epidermal and mucosal lesions due to herpes zoster. It has not had major effect on the pain associated with herpes zoster

Advances in Dental Pain Management

I.

Approach to Drug Tx in Pain

ANALGESIC LADDER (Adapted from WHO & Canadian Guidelines for CNCP)[4,5]

Used for both acute & chronic pain

Taper / Titrate

Non-opioids:
Acetaminophen
ASA / NSAID
+/- adjuvant*

Persistent or increasing pain

Opioid for Mild to Mod Pain:
Codeine,
Tramadol,
Buprenorphine patch

+/- non-opioid
+/- adjuvant*

Persistent or increasing pain

Opioid for Mod to Severe Pain:
Morphine,
Hydromorphone,
Oxycodone,
(?Tapentadol)

+/- non-opioid
+/- adjuvant*

Opioid for Mod to Severe Pain:
Morphine,
Hydromorphone,
Oxycodone
Fentanyl Patch**
if chronic stable pain; & unable to take oral
Methadone**
useful in patients with pain &/or addiction; useful, complex drug & requires special license
---
+/- non-opioid
+/- adjuvant*

AVOID Meperidine! DEMEROL; Poor analgesia, short acting, toxic metabolites, ↑ abuse risk.

⇨Use non-pharmacologic tx approaches concomitantly with drug tx to address the multifaceted aspects of pain & suffering!!!

*Potential Adjuvants in acute pain: TCA, gabapentin, ketamine, local anesthetics spinal epidural, nerve blocks, local freezing, corticosteroids & nondrug tx. (Includes drugs that treat pain directly, & drugs to manage the side effects of opioids.)

**NOT for opioid-naïve, generally NOT used for tx of acute pain

CNCP=chronic non-cancer pain CP = Chronic Pain ER MD=emergency physician fx=function FP=family physic
PIP=Prescription Information Program (SK) **Exit Strategy**: developed in concordance with physicians in Saskat

COMMON DRUG TREATMENT: INITIATION Considerations

1) **Acetaminophen** {325-500-650-1000mg PO q4-6h; MAX 4g/day}
   - ⇨often useful, given regular or PRN, for mild-moderate pain
   - ⇨can be given together with/or in addition to other analgesics
   - ⇨safe & few AEs in most; caution in overdose & severe liver dx
2) **NSAIDS** {ibuprofen, naproxen, celecoxib, others (see chart-pg 69)}
   - ⇨analgesic + anti-inflammatory with adequate/routine dosing
   - ⇨caution if high risk for GI ulcer/bleed PPI, renal dx,or cardiac dx
   - ⇨using with opioids allows for lowering of opioid dose *opioid sparing*
3) **Opioids** *Use Opioid Manager Tool* http://nationalpaincentre.mcmaster.ca/opioidmanager/
   - ⇨Frame as "trial": dependant on ↑ fx, AEs tolerable, no abuse
   - ⇨Assess Opioid Risk (ie. Opioid Risk Tool): take precautions in those with addiction hx or those at high risk. [a) need for Tx Agreement, b) baseline & routine UDS, c) check Rx Hx (ie. PIP)]
   - ⇨Avoid excessive quantities that could be misused.
   - [assess expected duration of need for drug; consider Rx for part fills]
   - ⇨Consider opioid naïve if on <60mg/day MEQ for <7 days
4) **Acute pain** is – SHORT term; either it will progress to chronic or subside & patient will return to baseline; prescribers must have plan in place for each patient & BE PREPARED for periods of TRANSITION ie. discharge from hospital, **opioid exit strategy**.
   - ⇨*CHOOSE* treatment modality(s) & *EDUCATE* patient
   - ⇨*ASSESS & DOCUMENT* progress
   - ⇨*COMMUNICATE* within circle of care

Address pt expectations: realistic 30-50% ↓ pain.

Dose-Response for Three Types of Oral Analgesics

- Opioids provide unlimited pain relief but side effects and abuse potential limit their use in ambulatory patients
- Ibuprofen and equi-analgesic oral doses of other NSAIDs provide a ceiling analgesic effect. Increasing beyond ibuprofen 400mg DOES increase anti-inflammatory effect which is an essential component of acute dental pain.
- ASA/APAP provide a lower ceiling analgesic effect which reaches maximum analgesic at 1000mg.
- APAP combined with NSAIDs shows a synergistic effect on acute dental pain and these two agents should be dosed concomitantly to maximize non-opoid pain control for acute dental pain.

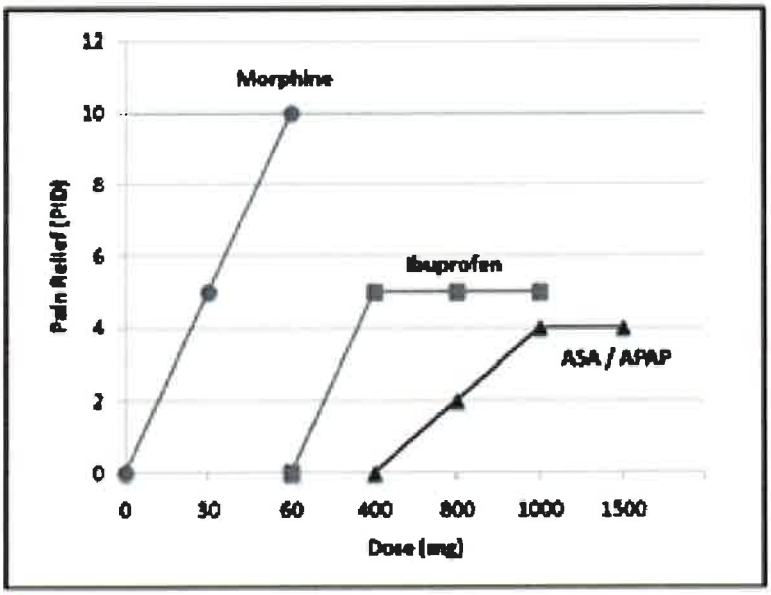


Figure 2. Analgesic efficacy. This graph illustrates a typical dose-response curve for orally administered (PO) analgesics. The dose-response curve for opioids such as morphine demonstrates unlimited efficacy in which greater doses provide greater analgesia. At equipotent doses, all opioids demonstrate a similar dose response. In contrast, nonopioids demonstrate a "ceiling" effect that generally is adequate for relief of mild to moderate pain (pain relief rating of 4–5 in this scale). For ibuprofen, doses greater than 400 mg do not provide further analgesia. For aspirin (ASA) and acetaminophen (APAP), this ceiling effect is achieved at 1000 mg and is somewhat lower than that provided by nonsteroidal anti-inflammatory drugs (NSAIDs).

II. ACETAMINOPHEN (APAP, Tylenol, g)

Maximum daily dosage:

- *ACUTE THERAPY*: Maximum of 4 g/day monitored and 3g/day unmonitored
- *CHRONIC THERAPY +/or ELDERLY PATIENT*: Maximum of 2.6 grams APAP/day

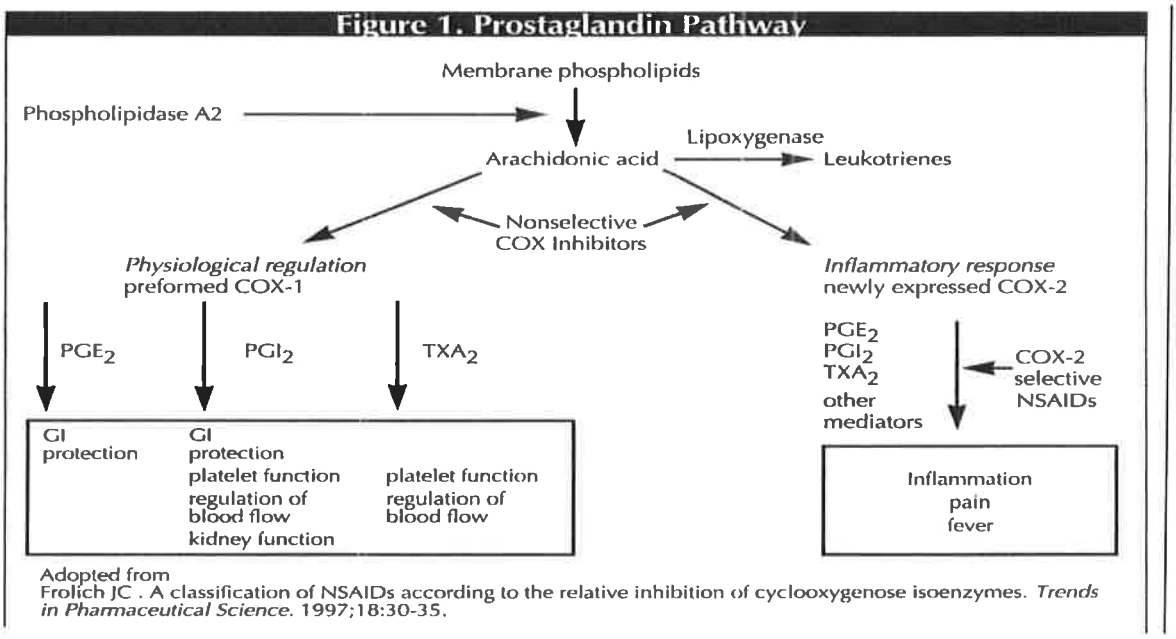
PRODUCT	***DOSAGE***	***ACUTE***	***CHRONIC***
Regular Strength APAP	325mg	12/day	8/day
Extra Strength APAP	500mg	8/day	5/day
Extended Relief APAP	650mg	6/day	4/day

Toxicity risk is increased by:

- *Fasting during acetaminophen therapy*
- *3 or more alcoholic drinks per day*

TOXICITY: ORAL: Ingestions of 200 mg/kg or 10 g, whichever is less, are considered potentially toxic. IV: A 10 fold overdose caused hepatotoxicity in a chronically malnourished child. THERAPEUTIC DOSE: ADULT: Oral: 650 to 1000 mg every 4 hours up to 4 g/day. IV: (50 kg or greater): 650 to 1000 mg every 4 to 6 hours, up to 4 g/day; (less than 50 kg): 12.5 mg/kg to 15 mg/kg every 4 to 6 hours, up to 3750 mg/day (75 mg/kg/day). PEDIATRIC: Oral: 10 to 15 mg/kg every 4 hours up to 60 mg/kg/day. IV: 12.5 mg/kg to 15 mg/kg every 4 to 6 hours, up to 75 mg/kg/day.

III. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (Non-acetylated)



Adopted from
Frolich JC . A classification of NSAIDs according to the relative inhibition of cyclooxygenose isoenzymes. *Trends in Pharmaceutical Science.* 1997;18:30-35.

A. NSAIDS COMMONLY USED FOR ACUTE PAIN AND INFLAMMATION

NSAID	*ROLE in Therapy* *	*Tp (hr)*	*t 1/2 (hr)*	*ANALGESIC Onset (hr)*	*Duration (hr)*	*USUAL ADULT DOSE (mg)*	*MAX. DAILY DOSE (mg)*
PROPRIONIC ACIDS							
flurbiprofen (Ansaid G)	P	1.5	5.7	2	6-7	50-100 q4-6h	300
ibuprofen (Motrin,G,otc)	P	1-2	1.8-2.	.5	4-6	400-600 q4-6h	3200/1200
ketoprofen (Orudis,OTC,G)	P,I	.5-2	2-4	1	6-7	50 q6-8h	300/75
naproxen(Naprosyn,G)	P,I	2-4	12-15	1	up to 7	500 stat, then 250 q6-8h	1500
naproxen Na (Anaprox,DS,G)	P,I	1-2	12-13	1	up to 7	550 stat, then 275 q6-8h	1650
naproxen Na (Aleve – OTC,G)	P,I	1-2	12-13	1	up to 7	440 stat, then 220 q 8-12h	660
ACETIC ACIDS							
diclofenac K(Cataflam)	P,I	1-2	1-2	.5	4-6	100 stat, then 50 q6-8h	200
diclofenac Na (Voltaren,G)	P,I	2-3	1-2	1	4-6	50 q6h	200
etodolac (Lodine,G)	P	1-2	7.3	.5	4-12	200-400 q6-8h	1200
ketorolac (Toradol oral,G)	P	.5-1	3.8-6	.5	6-8	20 stat, then 10 q4-6h	40
nabumetone (Relafen,G)	P,I	2-4	24	4 2	up to 12	750-1000mg q 12h	2000
SALICYLATE							
diflunisal (Dolobid,G)	P,I	2-3	8-12	1	8	1000 stat, then 500 q8h	1500
COX-2 SELECTIVE							
Celecoxib (Celebrex)	I	3	11	2	up to 24h	100-200mg 1d-bid	400

***P=pain relief, I=inflammation reduction**

B. CLINICAL APPLICATIONS:

1. *NSAIDS VS OPIOIDS*

ADVANTAGES OF PRESCRIBING NSAIDS	*DISADVANTAGES OF NSAIDS*
no sedation, constipation or respiratory depression	GI irritation is common
reduced swelling and trismus	no adult liquid preps are available
no central nausea and vomiting side effects	patient expectations are not fufilled
no potential for abuse or habituation	no activity limitations or sedation
	possible increased risk of blood clots

2. *GENERAL PRESCRIBING GUIDELINES*

a) NSAIDS can be mixed with narcotics +/or acetaminophen for additional effects, not synergistic
b) *AVOID* NSAID + NSAID combinations:
- take medication history, including OTC agents
- no therapeutic advantage, deleterious effects on GI tract, platelets

c) NSAID failure - try switching chemical classes
-acetic acid derivatives are structurally different so switching may improve response

3. *PATIENT-SPECIFIC FACTORS*

ASPIRIN TRIAD	Asthma, chronic urticaria, nasal polyps = sensitivity triad.
ASTHMA	Avoid NSAIDS if one triggers asthma, avoid COX-2s
ELDERLY	Choose NSAID with short t ½ to avoid accumulation
GASTRITIS, ALCOHOLISM	Use cytoprotective agent prophylaxis, COX-2s are better
LIVER DISEASE	Avoid diclofenac and piroxicam (Feldene)
HIATAL HERNIA	AVOID ASPIRIN, caution with any NSAID, COX-2s are better
PUD	Caution with any agent, may need prophylaxis, COX-2s are better
POST-OP PAIN	Ketorolac very effective if substance abuse history
RENAL DISEASE	Caution, diflunisal may be best NSAID, COX-2s NO BETTER
MAJOR SURGERY	D/C ASA 1 week prior, D/C other NSAIDS 24 hours prior, COX-2 Agents DO NOT increase bleeding risk and don't have to be D/C'd.
PRADAXA THERAPY	AVOID NSAID THERAPY INCLUDING COX-2s
WARFARIN *THERAPY*	AVOID NSAID THERAPY. COX-2's increase bleeding due to a drug intx.

C. INDIVIDUAL AGENTS

1. *IBUPROFEN (Motrin, g)*

- Many dosage forms: 100mg caplet, 50 & 100mg chewable tablets, 100mg/5ml susp, gel caps
- still the best first line agent due to good safety profile and reliable efficacy in acute pain (Oxford League)
- 800mg q 6 hours can be given initially, no anti-inflammatory value in doses above 3200mg/day

2. *NAPROXEN SODIUM (Anaprox, Anaprox DS, G)*

-May give lowest risk of blood clots so safest for atherosclerosis or peripheral artery disease
-Longer half-life than ibuprofen so may accumulate in elderly but works for about 8 hours

3. *KETOROLAC (Toradol, g, Sprix Nasal Spray)*

MANUFACTURER PRESCRIBING GUIDELINES LIMIT USE OF ORAL TABLETS

- Prescribing guidelines limit tablet use in response to serious adverse events
- Manufacturer bears less responsibility for adverse outcomes if practitioner uses medication outside of labeling
- Emphasizes the importance of proper patient selection criteria for all NSAIDS

IV. TRAMADOL (Ultram, G, Ultracet - Ortho/McNeil, RYBIX ODT - Victory)

A. *MECHANISM OF ACTION:*
- unique complimentary dual mechanisms
- tramadol is a weak opioid receptor binder as well as an inhibitor of serotonin and norepinephrine reuptake
- no inhibition of prostaglandin synthesis
- **controlled substance Schedule IV as of 8/18/14/ FDA pregnancy category C**

B. *THERAPEUTIC USE: 100MG =ASA/codeine 650/60 for acute pain.*
COMBINATION: Ultracet = 37.5mg tramadol/325mg acetaminophen, Ultram ER

C. *ADVERSE REACTIONS:*

Dizziness	26%	Nausea 24%
Constipation	24%	Headache 18%
Sedation	16%	

D. *DRUG INTERACTIONS*

carbamazepine →→ reduced tramadol effectiveness
MAOI →→ possible sympathomimetic potentiation (AVOID TRAMADOL)
CYP206 inhibitor →→ increased tramadol levels – caution with Prozac, Paxil, Zoloft SSRIs
CNS depressants →→ increased tramadol sedation

E. *DOSAGE & ADMINISTRATION*
- 50-100mg q 4-6 hours prn pain to maximum of 400mg/day (max dose for pts > 75 years is 300mg/day)
- 100mg initially is more effective for severe pain
- Tramadol 50mg ODT (Rybix) gives faster onset and comes in a 50mg tablet with no generic

F. *PATIENT SELECTION CRITERIA*
- Patients on NSAIDs, Warfarin, Pradaxa. Eliquis, Xarelto or oral hypoglycemics
- Patients with history of histamine release with opiates or on hemodialysis
- Diagnosis of neuropathic pain or history of gastrointestinal ulceration
- Patients with an opiate dependence hx. Should **not** take tramadol – Controlled Substance Schedule IV
- Patients with severe allergic rx to CODEINE OR OTHER OPIATES should NOT take tramadol

V. OPIOID ANALGESICS

A. OPIOIDS COMMONLY USED ORALLY FOR MILD TO MODERATE PAIN

OPIOID AVAILABLE	EQUIANANALG. DOSE (MG)	PEAK (HR)	DURATION (HR)	COMMENTS	PRECAUTIONS
Codeine (avoid in pts. On $2D_6$ inhibitors* - Prozac, Paxil, Cymbalta)	40-60	1.5-2	4-6	10% transformed to morphine, not useful after 60mg q 3 hr	Impaired ventilation, asthma, high intracranial pressure
Hydrocodone (Vicodin-ES,HP, Lortab,Zydone,G)	5	2	4-6	not useful after 10mg q 3 hr	Most addictive Schedule 3 Health care providers are at risk of abuse
Meperidine (Demerol,G)	50	1-1.5	4-5	Biotransformed to normeperidine, a toxic metabolite, max dose 200mg/24 hours orally	Normeperidine can accumulate with repeated dosing – causing seizures, avoid in pts. on MAOIs
Oxycodone (Percodan, Percocet,G)	2.5	1	3-4	not useful after 10mg q 3 hr	always a C II substance as it causes euphoria

***Amiodarone, Cimetidine, Desipramine, Duloxetine,Fluoxetine, Paroxetine, Propafenone, Quinidine, Ritonavir**

Dosing and conversion chart for opioid analgesics

Drug	Equianalgesic Oral Dose	Equianalgesic Parenteral Dose	Starting Dose Adults ≥ 50 kg		Starting Dose Adults ≤ 50 kg	
			Oral	Parenteral	Oral	Parenteral
Morphine[1]	30 mg q 3-4 h	10 mg q 3-4 h	15-30 mg q 3-4 h	10 mg q 3-4 h	0.3 mg/kg q 3-4 h	0.1 mg/kg q 3-4 h
Codeine[2]	130 mg q 3-4 h	75 mg q 3-4 h	60 mg q 3-4 h	60 mg q 2 h IM or SQ	1 mg/kg q 3-4 h[3]	Not recommended
Fentanyl		0.1				
Hydromorphone	7.5 mg q 3-4 h	1.5 mg q 3-4 h	6 mg q 3-4 h	1.5 mg q 3-4 h	0.06 mg/kg q 3-4 h	0.015 mg/kg q 3-4 h
Hydrocodone	30 mg q 3-4 h	Not available	10 mg q 3-4 h	Not available	0.2 mg/kg q 3-4 h	Not available
Levorphanol	4 mg q 6-8 h	2 mg q 6-8 h	4 mg q 6-8 h	0.04 mg/kg q 6-8 h	0.02 mg/kg q 6-8 h[3]	0.02 mg/kg q 6-8 h
Meperidine	300 mg q 2-3 h	75 mg q 3 h	Not recommended	100 mg q 3 h	Not recommended	0.75 mg/kg q 2-3 h
Methadone (Acute)	20 mg q 6-8 h	10 mg q 6-8 h	20 mg q 6-8 h	10 mg q 6-8 h	0.2 mg/kg q 6-8 h	0.1 mg/kg q 6-8 h
Oxycodone	20 mg q 3-4 h	Not available	10 mg q 3-4 h	Not available	0.2 mg/kg q 3-4 h[3]	Not available
Oxymorphone	Not available	1 mg q 3-4 h	Not available	1 mg q 3-4 h	Not recommended	Not recommended
Opioid agonist-antagonist and partial agonist						
Buprenorphine	Not available	0.3-0.4 mg q 6-8 h	Not available	0.4 mg q 6-8 h	Not available	0.004 mg/kg q 6-8 h
Butorphanol	Not available	2 mg q 3-4 h	Not available	2 mg q 3-4 h	Not available	Not recommended
Nalbuphine	Not available	10 mg q 3-4 h	Not available	10 mg q 3-4 h	Not available	0.1 mg/kg q 3-4 h
Pentazocine	150 mg q 3-4 h	60 mg q 3-4 h	50 mg q 4-6 h	Not recommended	Not recommended	Not recommended

1 For morphine, hydromorphone and oxymorphone, rectal administration is an alternate route for patients unable to take oral medications, but equianalgesic doses may differ from oral and parenteral doses because of pharmacokinetic differences.

2 **Caution:** Codeine doses above 65 mg often are not appropriate, due to diminishing incremental analgesia with increasing doses but continually increasing constipation and other side effects.

3 **Caution:** Doses of aspirin and acetaminophen in combination opioid/NSAID preparations must also be adjusted to the patient's body weight.

B. CLINICAL USE OF NARCOTIC ANALGESICS

1. POTENCY ESCALATION

STEP 1. Maximize nonopioids

STEP 2. Add Opioids for "rescue"

STEP 3. Increase Opioid potency if needed

Rx: Codeine 30mg w/APAP 300mg
Disp: #20

Rx: Hydrocodone 5mg w/APAP 500mg (Vicodin,
Disp: #15 (10mg of Hy = 80mg of Codeine)
Sig: 1-2 tabs q 4-6 hrs prn pain. Take with food/milk

Rx: Oxycodone 5mg w/APAP 325mg (Percocet, G)
Disp: #15 (10mg of Oxy = 120-160mg of Codeine)
Sig: 1-2 tab2 q 4-6 hrs prn pain. Take with food/milk

PATIENT CAUTIONS/INSTRUCTIONS

STEP 1. Combine ibuprofen with acetaminophen

STEP 2. Add opioids for additional pain relief or rest

STEP 3. Increase potency only if uncomfortable at rest
- if vestibular or GI problems, try 1/2 dose with 1/2 dosing interval
- combine with NSAID (Ibuprofen 800mg q6h scheduled)

to provide **SYNERGISTIC** pain relief & for sleep
- consider APAP content of RX when

-hydrocodone/APAP is Schedule II as of 10/6/14

-oxycodone/APAP has always been Schedule II

NOTE: Percocet now comes in SIX combinations (2.5/325, 5/325, 7.5/325, 7.5/500, 10/325, 10/650)

C. FIXED OPIOID COMBINATIONS WITH IBUPROFEN – NOT RECOMMENDED!!

1. **OXYCODONE 5MG/IBUPROFEN 400MG (COMBUNOX)**
2. **HYDROCODONE 7.5mg/IBUPROFEN 200mg (VICOPROFEN)**

D. ALLERGY VS PSEUDO-ALLERGY

True allergies involve an immune response while other reactions can fall into either side effects or pseudoallergy, which is generally the result of histamine release but no actual immune response. Below are some groups of symptoms followed with points to take into consideration when a patient exhibits one or more of the symptoms.

If the following symptoms occur with respect to opioid administration, they are likely related to a pseudoallergy rather than a true IgE mediated drug allergy:

- ✓ Generalized flushing, itching, sweating
- ✓ Mild hypotension accompanied by nausea and/or vomiting
- ✓ Itching, flushing, or hives at injection/application site

Pseudoallergy reactions can be managed and/or minimized using the following strategies:

- Try nonopioid analgesic if mild pain (acetaminophen & NSAID given at the same time)
- Avoid codeine, morphine & meperidine as these are most likely to trigger pseudoallergy.
- Use a more potent opioid (drugs listed below from least to most potent):
- Meperidine < codeine < morphine < hydrocodone < oxycodone < hydromorphone < fentanyl
- If effective against pain and symptoms are mild, consider administering opioid with an antihistamine such as diphenhydramine 25mg preferably in liquid form 30min prior to opioid dose.
- Consider reduction in opioid dose with more frequent administration if tolerated.

Stepped Approach for Managing Postprocedural Ambulatory Dental Pain

- Schedule regular NSAID doses and start prior to no LA effect
- Add APAP to NSAID maximizing both doses on a schedule
- If above is inadequate, add an opioid in combination with APAP but caution on maximum APAP dosing NOT TO EXCEED 4g/24h
- DO NOT prescribe an opioid analgesic for patients already on chronic opiates.
- DO NOT prescribe an opioid analgesic for patients currently treated for opioid addiction or with an addiction history.
- Chronic opiate patients are best managed in conjunction with the physcian who prescribed the opiate on a regular basis.

Table 4. Stepped Approach for Managing Postoperative Pain*†‡

	Suggested Regimens
Step 1	Ibuprofen 400–800 mg tid/qid or equivalent NSAID *and/or* Acetaminophen (APAP) 500–1000 mg q4d
Step 2	Add any of the following to Step 1 regimen: Oxycodone 5–10 mg or Morphine 15 mg 1 or 2 tabs q4h PRN *or* Pentazocine/NX 50 mg or Tramadol 50 mg 1 tab q4h PRN *or* Use combinations, provided no APAP included in Step 1 HC/APAP 5–10/500 1 or 2 tabs q4h PRN *or* OC/APAP 5–10/500 1 or 2 tabs q4h PRN *or* Pentazocine/APAP 1 or 2 tabs q4h PRN *or* Tramadol/APAP 1 or 2 tabs q4h PRN

* Step 1 regimens generally are adequate for mild and most cases of moderate postoperative dental pain. They should be prescribed continuously, "around-the-clock"—not PRN. Effective patient education is absolutely essential if this is to be accomplished. "They must take the medicine even when they are NOT having pain." When this regimen proves inadequate, or when pain is anticipated to be more severe, Step 2 regimens can be added but should not replace those in Step 1.

† APAP indicates acetaminophen; HC, hydrocodone; and OC, oxycodone.

‡ Adapted from Becker and Phero.[48]

PEDIATRIC ANALGESIC DOSAGES FOR DENTAL PAIN

	ONSET (min)	PEAK (hrs)	DURATION (hrs)	PEDIATRIC DOSE (mg/day)	AVAILABLE PEDIATRIC PREPARATIONS
Non-Narcotics					
Acetaminophen (Tylenol, Tempra, Panadol, g.)	20-30	0.5-2	3-7	10mg/kg q 4-6 hrs (max 65mg/kg/day)	Oral Solution: 48-325mg/5ml Chewable tabs: 80 + 160mg Rectal supp: 120,125,325,650mg
Diclofenac (Voltaren -Na^+salt)	120	3	4-6	2-4mg/kg/day	Diclofenac EC tab 25, 50, 75mg Cataflam tab 50mg
(Cataflam- K^+salt)	30	1	4-6	(max 200mg/day)	Tablets:250, 500mg
Diflunisal (Dolobid, g)	60	2-3	4-7	10mg/kg q 8 hrs (max 1500mg/day)	Oral Susp: 100mg/5ml
Ibuprofen (Advil, Children's Motrin, Medipren, Nuprin, g)	20-30	1-2	4-6	5-10mg/kg q4-6 hrs (max 40mg/kg/day)	Chew tabs: 50, 100mg Caplet:100 ,200mg Tablets: 200,400,600,800mg Capsules: 25,50,75mg
Ketoprofen (Orudis, Oruvail, g) OTC-Actron, Orudis KT	30	1-2	4-6	0.5-1mg/kg q6-8 hrs (max 300mg/day)	Ext.Release (Oruvail) 200mg Oral Susp: 125mg/5ml
Naproxen (Naprosyn, g)	60	1-2	4-7	10mg/kg/day (max 1500mg/day)	Tablets: 250,375,500mg Tablets: 220,275, 500mg
Naproxen Na (Anaprox, DS, g)	60	1-2	4-7	11mg/kg/day (max 1650mg/day)	Caplets: 220mg
Narcotics					
Codeine (sulfate or phosphate) **(ultra-fast metabolizers can Suffer toxic effects)-BLACK BOX WARNING in children post tonsillectomy and/or adenoidectomy**	15-30	0.5-1	3-6	0.5mg/kg q4 hr (max120mg/day)	Codeine PO_4/promethazine oral syrup: 10mg +6.25mg/5ml Codeine/APAP elixir: 12mg/120mg per 5ml susp: 12mg/120mg/5ml Lortab Elixir: 2.5 HC + 167 APAP/5ml
Hydocodone (Hydrocet, Lorcet, Vicodin, Zydone, g)	15-30	0.5-1	4-8	0.1-0.2mg/kg q4-6h (max= 90mg/day)	Tabs: 5/500 (Vicodin, Lorcet,g) 2.5/500 (Lortab) 7.5/500 (Lortab 7.5) 7.5/650 (Lorcet Plus) 7.5/750 (Vicodin ES,)
Meperidine (Demerol, g) **(Safe choice for patient allergic to morphine/codeine group)**	15-45	1	4-5	1-3mg/kg q 3-4h (max 20mg/kg/day)	Tabs: 50,100mg Oral Soln: 50mg/5ml Mepergan Fortis: 50mg MPD/ 25mg promethazine

Drug Interactions Important in Clinical Dentistry

DENTAL DRUG	INTERACTING DRUG	RESULT/MANAGEMENT
ANTIBIOTICS		
Penicillins		
All Penicillins	Bacteriostatic antibiotics (clindamycin, erythromycin, tetracyclines)	Static agent may impair action of penicillins. Consult with other prescriber for modification.
Rare decrease in OC effectiveness with >48 hour s of antibiotic therapy. Recommend additional barrier contraception for the remainder of the Pill package.	Methotrexate (Rheumatrex, g)	High dose penicillins may decease MTX secretion. Monitor MTX.
	Oral contraceptives	Rare decrease in estrogen effect. Use barrier contraception for duration of pill cycle.
	Probenecid (Benemid, g)	Tubular secretion of penicillins may be decreased. Usually not problematic.
Ampicillin	Allopurinol (Zyloprim, g)	Doubling in rate of ampicillin rash with concurrent administration (14-22%)
	Atenolol (Tenormin, g)	Atenolol bioavailability may be reduced.
Cephalosporins		
All Agents	Anticoagulants (Coumadin, g)	Risk of bleeding disorders might be increased in anticoagulated patients. Use cautiously.
	Bacteriostatic antibiotics (clindamycin, erythromycin, tetracyclines)	Static agent may impair action of cephalosporins. Consult with other practitioner for modification.
	Probenecid (Benemid, g)	Tubular secretion of penicillins may be decreased. Usually not problematic.
Cefdinir (Omnicef) Cefpodoxime (Vantin) Cefuroxime (Ceftin)	Increased gastric Ph. (Antacids, Axid, Pepcid, Prilosec, Tagamet, Zantac)	Reduced absorption of the cephalosporins. AVOID CONCURRENT USE.
Lincomycins		
Clindamycin (Cleocin, g)	Erythromycin	Possibility of antagonism. AVOID CONCURRENT USE.
	Kaolin-Pectin	Delay in clindamycin absorption with concurrent use.
	Succinylcholine (Anectine)	Possibility of prolonged respiratory depression. Monitor patient.
Macrolides/Azalides	Alfentanil	Alfentanil actions increased. Use caution.
Azithromycin (Zithromax,Zpak,g) –only agent that does not inhibit CYP450 3A4 but DOES prolong QT interval so only QT prolongation interactions apply to Azithromycin	Anticoagulants (Coumadin, g)	Risk of bleeding disorders is increased in anticoagulated patients. Monitor pt.
	Benzodiazepines (alprazolam, diazepam, triazolam)	Increased benzodiazepine levels resulting in CNS depression. Avoid combination in elderly.
dirithromycin (Dynabac) clarithromycin (Biaxin, Biaxin XL, g) erythromycin (base, EC, EES, PCE)		
	Bromocriptine (Parlodel)	Increase in bromocriptine toxic effects. Consult MD.
	CCBs (diltiazem (Cardizem,g) and verapamil (Isoptin, Calan, Verelan,g)	QT interval prolongation, sudden death, AVOID CONCURRENT USE
	Carbamazepine (Tegretol, g)	Increased carbamazepine levels. Avoid concurrent use. Azithromycin is okay.
	Clindamycin	Possible antagonism. AVOID COMBINATION.
	Cyclosporine (Sandimmune, Neoral)	Increased cyclosporine renal toxicity. Consult MD.
	Digoxin	Increased digoxin levels in 10% of patients. May use cautiously.
	Disopyramide (Norpace, g)	Increased disopyramide levels may cause arrhythmias. Use cautiously.

Macrolides All Age	Ergotamine	Acute ergotamine toxicity. Use cautiously
	Methylprednisolone	Steroid clearance may be decreased. Caution.
	Omeprazole (Prilosec)	Avoid Clarithromycin with Prilosec
	Penicillins	possible antagonism. Avoid static with cidal
	Pimozide (Orap)	Avoid all macrolides-risk of sudden death AVOID CONCURRENT USE
	"Statins" (Lipitor,Zocor, Mevacor)	Increased statin levels with possible muscle toxicity. AVOID CONCURRENT USE
	Theophyllines	Increased theophylline levels (20-25%). Decreased erythromycin levels may also occur. AVOID CONCURRENT USE if possible. SBE prophylaxis should not cause problems.
	Tolterodine (Detrol)	Increased Detrol effects causing arrhythmias
Metronidazole (Flagyl, Flagyl ER, Prostat, g)	Anticoagulants (Coumadin)	Risk of bleeding disorders is increased in anticoagulated patients. Consult MD.
	Barbiturates	Decreased metro. Levels. Increase dose.
	Cholestyramine (Questran, g)	Reduced absorption of metronidazole
	Cimetidine (Tagamet, g)	Metronidazole levels may increase. Not sig.
	Disulfuram (Antabuse)	Concurrent use may result in acute psychosis or confusion.
	Ethanol (IV diazepam, IV TMP-SMZ)	Risk of disulfuram-type reaction. AVOID CONCURRENT USE.
	Lithium	Increased lithium levels with possible toxicity. Consult MD.
	Phenytoin (Dilantin)	Eff. of phenytoin may be incr. Monitor closely.
	Quinidine	Increased Quinidine levels. Monitor closely.
	Tacrolimus (Prograf)	Metronidazole doubles Prograf levels
Tetracyclines		
All Agents (doxycycline, minocycline, tetracycline)	Antacids containing Al, calcium, magnesium	Reduced serum concentrations of tets. Space administration by 1-2 hours.
	Bismuth (Pepto-Bismol)	Inhibition of tetracycline absorption. Avoid concomitant administration.
	Iron Salts	Decreased absorption of tets. Space use by 2-3h.Doxy always affected.
	Oral Contraceptives	Slightly increased risk of ovulation. Use additional method during cycle.
Doxycycline (Vibramycin, Periostat??)	Carbamazepine (Tegretol)	Metabolism of doxy increased. Monitor response to doxycycline.
	Methotrexate (highdose IV)	AVOID DOXYCYCLINE WITH IV METHOTREXATE
	Phenobarbital	Decreased serum levels and effect of doxy. Monitor clinical response.
	Phenytoin (Dilantin, g)	Phenytoin stimulates doxy metabolism. Increase doxy dose or use other tet.
Tetracycline (Sumycin, Panmycin)	Colestipol (Colestid)	Colestipol binds tet in intestine. Do not administer concomitantly.
	Food (Milk and Dairy)	Decreased absorption of tet. Space use by 2-3 hours.
	Zinc sulfate	Tetracycline absorption is decreased. Space use by 2-3 hours.
Quinolones		
All Agents:	Antacids	Decreased quinolone absorption. AVOID
Ciprofloxacin (Cipro,g)	(iron, sucralfate, zinc)	CONCURRENT USE.
Gatifloxacin (Tequin)	Anticoagulants (Coumadin, g)	Increased risk of bleeding disorders. Monitor
Levofloxacin (Levaquin)		INR.
Moxafloxacin (Avelox)	Antineoplastics	Quinolone serum levels may be decreased.
Ofloxacin (Floxin)	Cimetidine (Tagamet, g)	Quinolone serum levels may be increased.
Sparfloxacin (Zagam)	Cyclosporine (Sandimmune, Neoral)	Cyclosporine renal toxicity may be enhanced.
Trovafloxacin (Trovan)	NSAIDs	Enhanced CNS stimulation
	Probenecid (Benemid, g)	Quinolone serum level may be increased50%.
	Theophylline	Increased theophylline toxicity possible with
	Caffeine	Cipro and other. Consult MD
Ciprofloxacin		Increased caffeine effects are possible.

ANTIFUNGALS	Anticoagulants (Coumadin)	Increased risk of bleeding disorders in anticoagulated patient. Consult MD.
Systemic Azole Agents (fluconazole, itraconazole, ketoconazole)		
	Benzodiazepines	Alprazolam, triazolam are contraindicated with itraconazole and ketoconazole. AVOID
	Cyclosporine (Sandimune, Neoral)	Increased cyclosporine levels. Can be used to the patients advantage.
	Rifampin	Decreased levels of the antifungal. AVOID CONCURRENT USE.
	Quinidine	30x increase in Quinidine. AVOID COMBO
	"Statins" (Crestor,Lipitor, Mevacor,Zocor, etc.)	Increased levels and SE of statins.
	Terfenadine (not available in the U.S.)	Increased terfenadine levels resulting in serious cardiac arrhythmias. AVOID CONCURRENT USE.
	Tolterodine (Detrol, Detrol LA)	Increased Detrol-causing arrhythmias.AVOID
	Zolpidem (Ambien)	Increased Ambien effect. Caution.
fluconazole (Diflucan)	Cimetidine (Tagamet, g)	Reduced fluconazole levels. AVOID CONCURRENT USE.
	Hydrochlorothiazide	Increased fluconazole levels.
	Losartan (Cozaar, Hyzaar)	Increased Losartan hypotension effect
	Oral Contraceptives	Decreased estrogen levels. AVOID CONCURRENT USE.
	Phenytoin (Dilantin, g)	Increased phenytoin levels. Monitor carefully.
	Sulfonylureas	Increased hypoglycemic effect. Monitor blood glucose.
itraconazole (Sporonax)	Digoxin	Increased digoxin levels. AVOID COMBINATION.
	Increased gastric pH	Reduced itraconazole levels
	Isoniazid (INH)	Reduced itraconazole levels
	Losartan (Cozaar)	Increased Losartan hypotension effect
	Sulfonylureas	Increased hypoglycemic effects. Monitor blood glucose.
ketoconazole (Nizoral, g)	Corticosteroids	Possible increase in steroid levels.
	Increased gastric pH	Decreased ketoconazole levels. AVOID CONCURRENT USE.
	Isoniazid (INH)	Decreased ketoconazole levels
	Theophyllines	Decreased theophylline levels. Consult with MD.
NON-NARCOTIC ANALGESICS		
NSAIDS		
(including aspirin and COX-2s)	Anticoagulants (apixaban, dabigatran,rivaroxaban,warfarin)	Increase risk of bleeding disorders in anticoagulated patient. Consult MD.
	Antihypertensives (all but CCBs) (ACEI,B-blockers, diuretics)	Decreased antihypertensive effect. Monitor Blood Pressure.
	Cimetidine (Tagamet, g)	NSAID levels increased/decreased
	Cyclosporine (Neoral, Sandimmune)	Nephrotoxicity of both agents may be increased. Avoid if possible.
	Fluoroquinolones	Increased CNS stimulation
	Lithium	Increased lithium levels. Use sulindac
	Methotrexate (Rheumatrex, Mexate)	Toxicity of methotrexate may be increased. Monitor.
	Phenytoin (Dilantin, g)	Increased phenytoin levels
	Probenecid (Benemid, g)	Increased toxicity of NSAIDs possible.
	Salicylates	Decreased NSAID levels with increased GI effects. AVOID CONCURRENT USE.
	SSRIs	Possible increased risk of bleeding but not thought to be clinically significant
COX-2 SELECTIVE NSAID		
Celecoxib (Celebrex)	$2C_9$ inhibitors (fluconazole)	Increased celecoxib levels

Ibuprofen (Motrin, g)	Digoxin	Possible increase in digoxin levels.
Ketorolac (Toradol,g)	Salicylates	Increased Ketorolac free drug conc.
Sulindac	DMSO	Decreased sulindac effectiveness and severe peripheral neuropathy. Avoid concurrent use.
Sulindac	Lithium	Lithium levels remain constant or decrease.
Acetaminophen only	Barbiturates, Carbamazepine, Phenytoin, Rifampin, Sulfinpyrazone	The hepatotoxicity of APAP may be increased by high dose or long term administration of these drugs.
	Cholestyramine (Questran, g)	Decreased APAP absorption. Do not administer within 2 hours of each other.
	Ethanol	Increased hepatotoxicity of APAP with chronic ethanol ingestion.
Tramadol (Ultram, Ultracet, g)	Any drug that enhances serotonin activity(SSRI antidepressants,"triptans" for acute migraine	Possible serotonin syndrome. AVOID CONCURRENT USE.
	Carbamazepine (Tegretol,g)	Decreased tramadol levels
	MAOI's (Marplan, Nardil, Parnate)	MAOI toxicity enhanced
	Quinidine	Tramadol increased/metabolite decreased
	Ritonavir (Norvir)	Increased Tramadol effect. AVOID COMBO.
NARCOTIC ANALGESICS		
Opioid analgesics	Alcohol, CNS depressants, local anesthetics, antidepressants, antipsychotics, antihistamines, cimetidine	Increased CNS and respiratory depression may occur. Use cautiously.
	Antimuscarinics and antidiarrheals (e.g. atropine), antihypertensives (e.g. guanadrel)	Opioids increase the effects of these drugs. Use cautiously.
	Buprenorphine, nalbuphine, naltrexone	These drugs block the analgesic effects of opioids. Substitute with NSAIDs.
Codeine	$2D_6$ Inhibitors, Amiodarone, Cimetidine, Desipramine, Fluoxetine, Paroxetine, Propafenone, Quinidine, Ritonavir	Inhibition of biotransformation of Codeine to active analgesic form. Use different narcotic on $2D_6$ Inhibitor patients.
Meperidine (Demerol, g)	MAOIs (Marplan, Nardil, Parnate, Furoxone) selegiline (Eldepryl)	Hypertension/hyperpyrexia or coma and hypotension.**AVOID CONCURRENT USE** if MAOI taken within 14 days.
	Protease inhibitors	Increased CNS/resp. depression- AVOID
	Ritonavir (Norvir)	Large increase in meperidine. AVOID COMBO.
Propoxyphene (Darvon, Darvocet, g)	Carbamazepine (Tegretol)	Carbamazepine metabolism is decreased.
	Protease inhibitors	Increased CNS/resp. depression- AVOID
LOCAL ANESTHETICS	Alcohol,CNS depressants,opioids, antide-pressants,antipsychotics, antihistamines	Increased CNS and resp. depression may occur. Use caution.
	Antiarrhythmic drugs	Increased cardiac depression.
Amides (e.g. lidocaine)	Beta Blockers, cimetidine	Metabolism of lidocaine is reduced. Use caution
Esters (e.g. procaine)	Anticholinesterases (Neostigmine) Sulfonamides	Metabolism of esters reduced. Inhibit sulfonamide action.
VASOCONSTRICTORS (epinephrine,levo-nordefrin)	Inhalation anesthetics (halothane)	Increased chance of arrhythmia
	Tricyclic antidepressants-high dose (amitriptyline, desipramine, imipramine, nortriptyline, etc)	Increased sympathomimetic effects possible. Limit epi to 0.04mg with high dose TCA's.
	Beta-blockers (nonselective)	Hypertensive and/or cardiac rx possible.
	(e.g. propranolol, nadolol)	Limit epi to 0.04mg/2hr. visit.
	Phenothiazines (e.g. chlorpromazine)	Vasoconstrictor action inhibited,leading to possible hypotensive responses. Use cautiously.
	Monoamine Oxidase Inhibitors (MAOIs)	Slight possibility of hypertensive rx.
	Selegiline (Eldepryl,g)	Slight possibility of hypertensive rx.
	COMT Inhibitors (Comtan, Tasmar)	Slight possibility of hypertensive rx.

AGENTS FOR PARENTERAL ANESTHESIA		
Antihistamines		
diphenhydramine (Benadryl) hydroxyzine (Atarax, Vistaril) Promethazine (Phenergan)	Anticholinergics	Increased dry mouth, tachycardia, urinary retention. Monitor.
	CNS depressants (alcohol, narcotics)	Enhanced duration and intensity of sedation. Reduce dosages.
Barbiturates		
methohexital (Brevital,g)	CNS depressants (alcohol, narcotics)	Additive CNS and resp. depression
	Furosemide (Lasix, g)	Orthostatic hypotension
	Sulfisoxazole IV	Sulfa competes with barb. for binding sites. Smaller and more frequent barb. doses may have to be given.
Benzodiazepines		
diazepam (Valium,G)	CNS depressants (anticonvulsants, alcohol)	Oversedation so may use slower titration.
	Cimetidine,OCs,INH,Ketoconazole, Metoprolol, Omeprazole, Propoxyphene, Propranolol,Valproic Acid	Decreased clearance of diazepam. Can avoid with lorazepam.
	Digoxin	Increased digoxin levels.
midazolam (Versed,g)	Calcium Channel Blockers or CCBs (diltiazem-Cardizem, verapamil-Isoptin,Calan, Verelan)	CCBs inhibit Cyp3A4 which prolongs the actions of midazolam. Evaluate patient factors to determine clinical significance.
	CNS depressants (alcohol, barbs)	Increased risk of underventilation or apnea. May prolong the effect of midazolam.
	Erythromycin	Increased midazolam levels. Monitor.
	Inhalation anesthetics	Midazolam decreases MAC of halothane
	Narcotics (morphine, meperidine, fentanyl)	Increased hypnotic effect of midazolam. More hypotension with Versed and Demerol.
	Saquinavir (Fortovase)	Increased midazolam levels. AVOID COMBO.
	Thiopental	After premed with Versed, decrease dose of thiopental for induction by 15%
Narcotics		
fentanyl (Sublimaze,g)	Barbiturate anesthetics	Additive CNS and resp. depression.
	Chlorpromazine (Thorazine, g)	Increased toxicity of both agents.
	Cimetidine (Tagamet, g)	CNS toxicity case reports only. (confusion, apnea, seizures)
	Diazepam	With high dose fentanyl gives CV depression.
	Droperidol (Inapsine)	Hypotension and decreased pulmonary arterial pressure.
	Nitrous Oxide	With high dose fentanyl may cause CV depress.
	Ritonavir (Norvir)	Increased fentanyl levels with Norvir
meperidine (Demerol, G)	Barbiturate anesthetics	Additive CNS and resp. depression
	Chlorpromazine (Thorazine, g)	Increased toxicity of both agents.
	Cimetidine (Tagamet, g)	CNS toxicity as with fentanyl.
	MAOIs and furazolidone (Furoxone)	Meperidine has predictable and sometimes fatal reactions with use within 14 days. Type1 :coma,resp dep,cyanosis,low BP Type2:seizures,hyperpyrexia,hypertension,tachy-cardia. AVOID CONCURRENT USE!!!!!
	Phenytoin (Dilantin, g)	Decrease meperidine effects by increased hepatic metabolism
Miscellaneous		
etomidate (Amidate)	Verapamil	Possibility of prolonged anesthesia
ketamine (Ketalar,g)	Barbiturates	Prolonged recovery time.
	Halothane	Halothane blocks the CV stimulate effect of ketamine.Closely monitor cardiac function.
	Thyroid Hormone	May produce hypertension/tachycardia
	Tubocurarine and nondepolarizing muscle relaxants	Ketamine may increase neuromuscular effects and result in prolonged resp. depression.
Propofol (Diprivan, G)	CNS depressants (sedative/hypnotic, inhalation anesthetics, narcotics)	Increase CNS depression of propofol. Premed with narcotics may lead to more pronounced decrease in systolic, diastolic, and mean arterial pressures and cardiac output.

DRUG-INDUCED QT INTERVAL PROLONGATION RECOGNITION AND AVOIDANCE

What risk factors for drug-induced QT prolongation and TdP are present in the patient? Are any risk factors modifiable?

As mentioned in Part I and in a scientific statement by the American College of Cardiology (ACC) and American Heart Association (AHA), there are numerous known risk factors for drug-induced TdP including:[1,2]

- A QTc interval >500 msec or an increase in QTc interval by >60 msec compared to baseline
- Genetic predisposition – ion channel mutations leading to congenital QT prolongation
- Heart disease including heart failure and myocardial infarction
- Bradycardia
- Female gender
- Advanced age
- Concomitant administration of >1 drug known to cause QT prolongation or TdP*
- Hypokalemia or hypomagnesemia*
- Rapid intravenous (IV) infusion of a drug known to cause QT prolongation or TdP*
- Drug interactions or organ dysfunction (hepatic, renal) that cause elevated plasma drug levels*
- History of drug-induced TdP

*Modifiable risk factors

QT Prolonging Medications

Antimicrobials	Antidepressants	Antipsychotics	Anticonvulsants	Other Drugs
Atazanavir	Amitriptyline	Chlorpromazine	Felbamate	Moexipril
Azithromycin	Citalopram	Clozapine	Fosphenytoin	Nilotinib
Bactrim	Clomipramine	Haldol	Phenytoin	Octreotide
Ciprofloxacin	Desipramine	Mesoridazine		Oxytocin
Chloroquine	Doxepin	Paliperidone	**Other Drugs**	Probucol
Clarithromycin	Escitalopram	Pimozide	Alfuzosin	Ranolazine
Erythromycin	Fluoxetine	Quetiapine	Astemizole	Sunitinib
Fluconazole	Nortriptyline	Risperidone	Amantadine	Tacrolimus
Foscarnet	Paroxetine	Sertindole	Bepridil	Tamoxifen
Gatifloxacin	Protriptyline	Thioridazine	Cisapride	Terfenadine
Gemifloxacin	Sertraline	Ziprasidone	Diphenhydramine	Tizanidine
Halofantrine	Trazodone		Eribulin	Vandetanib
Imipramine	Trimipramine	**Antiarrhythmics**	Famotidine	Vardenafil
Itraconazole	Venlafaxine	Amiodarone	Fingolimod	
Ketoconazole		Disopyramide	Galantamine	
Levofloxacin	**Antiemetics**	Dofetilide	Indapamide	
Moxifloxacin	Dolasetron	Dronedarone	Lapatinib	
Ofloxacin	Domperidone	Flecainide	Levomethadyl	
Pentamidine	Droperidol	Ibutilide	Lithium	
Ritonavir	Granisetron	Nicardipine	Methadone	
Sparfloxacin	Odansetron	Procainamide		
Telithromycin		Quinidine		
Voriconazole		Sotalol		