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. LEXI-COMP DRUG INFORMATION HANDBOOK FOR DENTISTRY – www.lexi.com
-2025 Handbook 30th ed. Final edition is $114.95, available for one or more office PCs as well
-UPTODATE Lexidrug Dental Mobile Pro Package is $199/year and includes Lexi-Interact
PDA/Android,iPhone,iPad,iTouch,,HP,PocketPC,PalmOS:**Dental Lexi Drugs is $75/year**

B. EPOCRATES (free) AND EPOCRATES RX PRO ($175/year) are useful in dental practice

C. DRUGS.COM and MEDSCAPE can supplement your online drug-related info at no charge

D. MOSBY'S DENTAL DRUG REFERENCE, 14th edition published November 2024 costs $58.39

III. SPECIFIC DENTAL DRUG RESOURCES

A. GUIDE TO ANTIMICROBIAL THERAPY 2024 (June every year) – www.sanfordguide.com
-desktop, spiral bound, softcover, PDA/Pocket PC versions available
-Spiral is $45.00, softcover is $35.00, don't buy on Amazon – use the Sanford Guide website

B. PEDIATRIC DRUG DOSAGE HANDBOOKS

1. Harriet Lane Handbook: 23rd Edition. $ 58.49 Mosby. May 2023 (published every 3 years)
2. Pediatric Lexi-Drugs for Blackberry by Lexi-Comp
3. LexiComp Pediatric & Neonatal Dosage Handbook 25th edition, $109.952023-2024

C. ANXIOLYSIS AND CONSCIOUS SEDATION HANDBOOKS

1. **Malamed Stanley. Sedation: A Guide to Patient Management. 7th edition, 2025, Elsevier Health Sciences ($107.99) and not available until 9/01/2025**
2. **Handbook of Nitrous Oxide and Oxygen Sedation. 6th edition, April 14, 2025 Mosby ($73.99)**

D. DENTAL MANAGEMENT GUIDES

1. **Malamed Stanley. Medical Emergencies in the Dental Office. 8th edition. 2022 (89.95)**
2. **Little and Falace. Dental Management of the Medically Compromised Patient. 10th edition. May 2023 (book-106.99, ebook – 86.95)**
3. **Malamed Stanley. Handbook of Local Anesthesia. 7th edition, June 2019. ($27.39-$88.28)**
4. **Dym, Harry. Clinical Pharmacology for the Oral and Maxillofacial Surgeon.1st ed. 2022**

IV. Herbal and Nutritional Drug Product References

A. Natural Medicines TRC Healthcare – www.naturalmedicines.therapeuticresearch.com
-best resource for health professionals and very detailed for $19/month.

B. Nutrition Action Health Letter – www.cspinet.org
-published by Center for Science in the Public Interest (CSPI) - $24/10 issues per year or $58 for 3 years

C. Other Useful Websites
-www.consumerlab.com-excellent resource & $45/year, www.quackwatch.com, naturowatch.com
-www.science-basedmedicine.org. www.supplement-clarity.com with author Joe Cannon, M.S.

Dental Management of the Medicated Patient

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Table A.1
ANTIHYPERTENSIVE MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
DIURETICS – thiazides are used for hypertension and loops are used mostly for Heart Failure and edema		
Thiazide-Type Chlorothiazide (Diuril,G) Chlorthalidone (Hygroton, G) Hydrochlorothiazide (Microzide 12.5mg,G) Indapamide (Lozol) Methyclothiazide (Enduron, G) Metolazone (Zaroxolyn, Mykrox)	-All agents can cause high uric acid, low K+, high blood sugar, low sodium, slight xerostomia, oral ulcerations -Chlorthalidone is becoming the diuretic of choice for hypertension due to longer duration and less dependence on renal fx for effect	-Oral lesions possible -NSAIDs decrease effect of diuretic. Prostaglandins enhance renal blood flow so any PG inhibitor can reduce diuretic effectiveness. Minimize effect by limiting duration to 3-5 days.
Loop Diuretics Bumetanide (Bumex,G) Furosemide (Lasix, G) Torsemide (Demadex)	Dehydration, low K+, high blood sugar, high uric acid, oral lichenoid lesions, most severe xerostomia of all diuretics	-Treat xerostomia -Identify oral ulcers -NSAIDs decrease effect of diuretic. Best choice is Diflunisal.
Potassium-Sparing Amiloride (Midamor, G) Spironolactone (Aldactone, G) Triamterene (Dyrenium,G)	High K+, gastrointestinal upset (GI)	-Increased gag reflex -NSAID's decrease amiloride effect -Concomitant Indomethacin with triamterene may cause renal failure. Avoid combo
Combination Diuretics Aldactazide (HCTZ + Spironolactone,G) Dyazide (HCTZ 25 + Triam 37.5, G) Maxzide-25 (HCTZ 25 + Triam 37.5, G) Maxzide (HCTZ 50 + Triam 75, G) Moduretic (HCTZ + Amiloride, G)	All of these combination diuretics are intended to minimize potassium depletion while providing good blood pressure reduction	See individual agents above
ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS-ACE BREAKS DOWN BRADYKININ IN LUNG →COUGH		
Benazepril (Lotensin,G) Captopril (Capoten, G) Enalapril (Vasotec, G) Fosinopril (Monopril,G) Lisinopril (Prinivil,Zestril,G) Moexipril (Univasc,g) Perindopril (Aceon) Quinapril (Accupril) Ramipril (Altace,g) Spirapril (Renormax) Trandolapril (Mavik,g)	HA, dizziness, fatigue,hypotension, loss of taste, oral ulcers, cough(highest with ramipril with 12% incidence) Early in therapy, reactions such as orofacial angioedema and "scalded mouth syndrome" can occur. Both of these reactions require discontinuation of the ACEI with little prospect of successful rechallenge	-Oral lesions possible -NSAIDs decrease effect -Caution with position change -Quinapril reduces Tetracycline absorption by 33% -ACEIs can cause hyperkalemia so patients should avoid salt substitutes which contain potassium and cardiac rate and rhythm changes should be investigated.
ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)		
Azilsartan (Edarbi)	HA,dizziness,cough (1%),	
Candesartan (Atacand,g)	HA, dizziness, cough (1%)	-NSAIDs decrease effect
Eprosartan (Teveten,g)	HA, dizziness, cough (2%)	-Caution with position change
Irbesartan (Avapro,g)	HA, dizziness, cough (2.8%)	-macrolides and azole antifungals may increase losartan levels
Losartan (Cozaar, Hyzaar,g)	HA, dizziness, cough (3.4%)	-Well tolerated but more expensive than ACE Inhibitors
Telmisartan (Micardis)	HA, dizziness, cough (1%)	
Valsartan(Diovan,g)	HA, dizziness, cough (1%}	-not much hypotension

CALCIUM CHANNEL BLOCKERS		
Amlodipine (Norvasc,g).....	...HA, dizziness, peripheral edema	-Diltiazem and Verapamil interact with macrolides resulting in QT interval prolongation and possibly SUDDEN DEATH!
Bepridil (Vascor).....	...Dizziness, nervousness, HA, GI, dry mouth	
Diltiazem (Cardizem/SR/CD,Dilacor XL,G).	...Same as Verapamil	-Caution with position change
Felodipine (Plendil).....	...Peripheral edema, HA dizziness, flushing, respiratory infections, cough	-Strict home care due to increased incidence and severity of gingival overgrowth with plaque build-up
Isradipine (DynaCirc).....	...Like nifedipine,less edema,dizziness	
Nicardipine (Cardene).....	...Same as Verapamil but more edema and tachycardia	-All CCBs may interact with Fentanyl causing hypotension
Nifedipine (Procardia XL, Adalat, G)....	...Peripheral edema, dizziness, HA, nausea, gingival hyperplasia	-All CCBs may inhibit platelet function-mainly nifedipine -Felodipine toxicity increased by erythromycin
Nislodipine (Sular,g)……..	…HA, dizziness, peripheral edema	-Felodipine interacts with grapefruit juice
Verapamil .....…….. (Calan/SR, Isoptin/SR, Verelan, G)	...Hypotension, dizziness, HA, bradycardia, gingival hyperplasia	-"pines"=reflex tachycardia and peripheral edema

PERIPHERAL ANTI-ADRENERGIC DRUGS		
Beta-Blockers		
+Acebutolol (Sectral, G).....	...Less bradycardia	-Cause problems in asthma, diabetes
+Atenolol (Tenormin, G).....	...Same as Propranolol	-Increased pressor response to epi worst with non-selectives and epi doses above 0.1mg or 5 carpules. Avoid interaction with selective agent, Labetalol, or Carvedilol.
+Betaxolol (Kerlone,G).....	...Same as Propranolol	
+Bisoprolol (Zebeta, Ziac w/HCTZ,G).....	...Same as Atenolol	
++Carteolol (Cartrol).....	...Less bradycardia, same as Propranolol	
+++Carvedilol (Coreg,g)*.....	...Dizziness, fatigue, hyperglycemia	-If patient takes a non-selective, limit epi to 0.04mg (++)
+++Labetalol (Trandate, Normodyne, G).....	...Orthostatic hypotension, same as Propranolol	-Propranolol and Metoprolol can increase Lidocaine and BZDP levels
+Metoprolol (Lopressor, Toprol XL,G)...	...Same as Propranolol	-Treat xerostomia
++Nadolol (Corgard,G).....	...Same as Propranolol	-Carvedilol safer with epi because of alpha blocking effect
+Nebivolol (Bystolic)……	…HA, dizziness, nausea, insomnia	
++Penbutolol (Levatol).....	...Less bradycardia, same as Propranolol	
++Pindolol (Visken, G).....	...Less bradycardia, same as Propranolol	
++Propranolol (Inderal, G).....	...Fatigue, bradycardia, GI, masks hypo-glycemia, sudden withdrawal can lead to rebound hypertension, xerostomia	
++Sotalol (Betapace,G).....		
++Timolol (Blocadren, G).....	...Same as Propranolol	
+Selective (Primarily blocks beta-1 in the heart)		+++Non-selective beta and alpha-1 blocker
++Non-selective (Blocks both beta-1 in the heart and beta-2 in the periphery)		* Indicated for mild to moderate CHF

ALPHA-ADRENERGIC BLOCKERS		
Doxazosin (Cardura,G).....	...Dizziness, HA, weakness, edema	-Oral lichenoid lesion with Prazosin
Prazosin (Minipress, G).....	...Dizziness, Vertigo, palpitations, HA	-NSAIDs reduce effectiveness
Tamsulosin (Flomax,G)*.....	...Dizziness, HA	-Caution with position change
Terazosin (Hytrin, G)).....	...Drowsiness, dry mouth, fluid retention	
*only indication is BPH		

CENTRAL ANTI-ADRENERGIC DRUGS		
Clonidine (Catapres, G)..... (Catapress TTS;transdermal)	...Rebound hypertension, HA, arrhythmias after sudden withdrawal, dry mouth, sedation ...Milder than Clonidine	-Oral lesions with Methyldopa -Xerostomia worst with Clonidine but is common for all four
Guanabenz (Wytensin).....	...Milder than Clonidine	-Increased pressor response to epi with Methyldopa
Guanfacine (Tenex,Intuniv,g).....	...Sedation, orthostatic hypotension,	-NSAIDs reduce effectiveness
Methyldopa (Aldomet, G).....	bradycardia, GI, oral lichenoid lesions, dry mouth, salivary gland pain	-Caution with position change

Table A-2
ANGINA PECTORIS MEDICATIONS [Beta-Blockers, Calcium Channel blockers see table A-1]

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
NITRATES		
Nitroglycerin -sublingual (Nitrostat, Nitroquick, G) -translingual (Nitrolingual) -oral, SR (Nitro-Bid, G) -topical ointment (Nitrol, G) -transdermal(Transderm-Nitro,Nitro-dur, Minitran, Deponit, G) -transmucosal cr, Nitrogard Isosorbide Dinitrate (Isordil, G) Isosorbide Mononitrate (Ismo, Imdur, Monoket)	Dizziness, orthostatic hypotension, flushing, HA, palpitations. -Patients should respond to SL nitro very rapidly and should be seated in an upright position while awaiting effect. -BP should be monitored and oxygen may be supplied to the patient. Give second dose if inadequate response after 5 min.	-Short, midday appointments -Premedication for stress reduction with BZDP or nitrous oxide -Limit epi to 0.04mg/2 hour visit -Keep sublingual nitro or spray in office -Do angina history often -Max office dose of nitro is 2 tabs,do not give third tablet if systolic BP < 90mmHg -Call 911 if chest pain not resolving after 10 minutes and 2 nitro tablets sublingually -Halitosis with Isosorbide Dinitrate

Table A-3
HEART FAILURE MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
FIRST LINE - ACE INHIBITOR	**-orthostatic hypotension, increased K+**	**-watch for cough, orthostatic hypotension**
FIRST LINE-BETA BLOCKER: carvedilol, bisoprolol, metoprolol succinate approved	**-epinephrine dose limitation due to diagnosis of HF and carvedilol or metoprolol**	**-may need to limit epinephrine due to disease state or noncardioselective BB**
FIRST LINE – DIURETIC – loops preferred	**Electrolyte abnormalities**	**-may not resolve peripheral edema**
FIRST LINE – ARB, ARNI (ARB & sacubitril)	**Orthostatic hypotension,increased K+, cough**	**-well tolerated and increasingly prescribed**
FIRST LINE – ALDOSTERONE ANTAGONIST: Eplerenone or Spironolactone	Possible high potassium levels,avoid with elevated Scr	**-well tolerated**
2nd LINE - hydralazine, isosorbide or ivabradine	-HA, dizziness, orthostasis, halitosis	**-indicates more severe/refractory heart failure**
LAST LINE - digoxin	-anoxrexia,GI,HA,bradycardia,vision changes	**-indicated after trying all other agents**

Table A-4
ANTIARRHYTHMIC MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
Amiodarone (Cordarone, Pacerone,G)	**...Oral Ulcers, neuralgic pain,Pulmonary tox.**	**-Amiodarone interacts with Fentanyl**
Digoxin (Lanoxin, G).....	**...Anorexia, GI, HA, bradycardia**	**causing hypotension, bradycardia**
Disopyramide (Norpace, G).....	**...Dry mouth, hypotension, GI, hypoglycemia**	**-Amiodarone may increase lidocaine levels**
Dofetilide (Tikosyn)……..	**…HA, chest pain, dizziness, arrhythmias**	**-Oral ulcers with procainamide**
Encainide (Enkaid).....	**...Bradycardia, dizziness, HA, GI**	**-Xerostomia- worst with disopyramide**
Flecainide (Tambocor,G).....	**...Bradycardia, dizziness, HA, GI, neutropenia**	**-Tikosyn levels increased by eryth/azoles**
Mexiletine (Mexitil).....	**...GI, fatigue, dizziness, tremor, blood dyscrasias**	**-Oral bleeding due to blood dyscrasias** **-Taste disturbances with Propafenone**
Procainamide (Pronestyl, G).....	**...Lupus-like syndrome, GI, hypotension, blood dyscrasias**	**-Local anesthetics increase CNS adverse effects of Propafenone**
Propafenone (Rythmol,G).....	**...Bradycardia, dizziness, GI, metallic taste**	**-Caution with position change/stress** **-Digoxin levels are increased by BZDP, Erythromycin, Tetracycline, Ibuprofen**
Sotalol (Betapace,G).....	**...QT,bradycardia,chest pain,fatigue**	**-Erythromycin increases disopyramide levels with resultant arrhythmias** **-Mexiletine absorption decr. by narcotics**

Table A-5
ANTIHYPERLIPIDEMIC MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
Alirocumab (Praluent injection)	**…nasopharyngitis, allergic reactions**	**-indicates high CV risk patient**
Atorvastatin (Lipitor,G)……	**...GI, HA**	**-Most cause taste disturbances**
Evolocumab (Repatha injection)	**…nasopharyngitis, allergic reactions**	**-indicates high CV risk patient**
Ezetimibe (Zetia)……..……..	**…GI, HA, flatulence**	**-Gag reflex is increased with all agents**
Fenofibrate (Tricor,G)……	**…GI, rash**	
Fluvastatin (Lescol,G).....	**...Upper Resp Infect,HA,GI,arthropathy**	**-Simvastatin,Pravastatin,Atorvastatin and**
Gemfibrozil (Lopid, G).....	**...GI, abnormal taste**	**Fluvastatin interact with macrolides &**
Lovastatin (Mevacor,G).....	**...HA, GI, Abnormal taste**	**azole antifungals increasing risk of severe**
Nicotinic Acid (Niacin, B_3).....	**...Flushing, itching, GI**	**myopathy. Avoid this combination.**
Pitavastatin (Livalo)……..	**…GI,muscle weakness,hypersensitivity**	
Pravastatin (Pravachol,G)……	**...GI, local muscle pain**	**-Colestipol reduces tetracycline level**
Rosuvastatin (Crestor).....	**…GI, muscle weaknes, abnormal taste**	
Simvastatin (Zocor,G).....	**... HA, GI**	

Table A-6
HEMOSTASIS MODIFIERS [# anti-platelet effect; @ anticoagulation effect] – SEE DENTAL MANAGEMENT GUIDE

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
Apixaban (Eliquis)@.....	**…Major bleed 1.5-1.7%,easy bruising**	**-ASA, antibiotics, Metronidazole, Azole**
Aspirin (G)#.....	**...GI disturbances, GI bleeding, tinnitus**	**antifungals inc. bleeding with warfarin**
Aspirin 25/Dipyridamole 200 ER (Aggrenox)#…	**…GI, bleeding,dizziness,tinnitus**	**-Clopidogrel levels increased by NSAIDs**
Clopidogrel (Plavix,G)#.....	**...Dizziness, GI upset**	**-Ticagrelor/Rivaroxaban toxicity increased by 3A4 inhibitors such as macrolides**
Dabigatran Etexilate (Pradaxa)@.....…	**…GI bleeding, monitor with ECT or PTT**	
Edoxaban (Savaysa)@……	**…Hypertension,nosebleed,major bleed 2.2%**	**-DC Ticagrelor/Rivaroxaban 5d prior to major surgery but consult MD for dental**
Prasugrel (Effient)#.....	**…Major bleed 2-5%,syncope,stroke risk if d/c**	
Rivaroxaban (Xarelto)@.....	**…Perisurgical bleeding may be prolonged**	**-Warfarin patients with INR 1.5 to 3.5 times normal can be managed without dose change but confirm surgery day.**
Ticagrelor (Brilinta)#……..		
Warfarin (Coumadin,G)@.....….	**...GI bleeding, monitor with INR,may use Tranexamic 5% mouthrinse 10ml 2min prior to surgery and every 6 hours for 48 hours to promote fibrin clot formation**	**-Consult MD before altering warfarin dose** **-AVOID NSAIDs WITH ANTICOAGULANTS**

Table B-1
ANTIDEPRESSANT MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
TRICYCLIC ANTIDEPRESSANTS (TCAs)		
Amitriptyline (Elavil, G) 4+ Clomipramine (Anafranil,G) 3+ Desipramine (Norpramin, G) 1+ Doxepin (Sinequan, G) 2+ Imipramine (Tofranil, G) 2+ Nortriptyline (Pamelor, Aventyl, G)1-2+ Protriptyline (Vivactil) 3+	Sedation, dry mouth, orthostatic hypotension, tachycardia. Greater than 100mg daily of the first five listed TCAs poses an interaction threat with epi so limit to 2.5 carps/2h visit Greater than 50mg daily of nortriptyline poses epi interaction threat so limit to 2.5 carps/2h visit	-Epi interacts with high-dose TCA therapy -Additive CNS depression with opioids and anti-anxiety agents -TCAs cause most severe xerostomia -Record baseline and post-treatment BP if vasoconstrictor is used -Quinolone antibiotics with TCAs may produce arrhythmias
MISCELLANEOUS ANTIDEPRESSANTS		
Nefazodone (Serzone, g) 2-3+……..	…risk of liver failure limits usefulness	-all increase CNS depression when combined with opioids
Trazodone (Desyrel, g) 1+……..	…increases serotonin, used for insomnia	
Vilazodone (Viibryd) 1+……..	…SSRI/serotonin receptor agonist for MDD	
SELECTIVE SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)		
Desvenlafaxine (Pristiq) 0+……	…Sedation, dizziness, less BP increase	-Additive CNS depressant effects with Trazodone and opioids
Duloxetine (Cymbalta,g) 0-1+……	….Nausea,dry mouth,constipation,fatigue	-Much less dry mouth than TCAs
Levomilnacipran (Fetzima) 0-1+…..	….Indicated for major depressive disorder	-Most likely to increase BP of all anti-depressant groups-dose related
Milnacipran (Savella) 0-1+…….	….Indicated for fibromyalgia only, nausea, fatigue,constipation,dizziness	-Most likely antidepressant group to be used for neuropathic or chronic pain
Venlafaxine (Effexor,g) 0-1+.....	....Dizziness, anxiety, tremor, BP increases	
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)		
Citalopram (Celexa,g) 0-1+……. Escitalopram (Lexapro,G) 0-1+..... Fluoxetine (Prozac, G) 0-1+..... Fluvoxamine (Luvox,g) 0-1+.....	…Nausea, dry mouth, sedation, insomnia ….reduced side effects, well tolerated ...HA, insomnia, irritability ...Insomnia,anxiety,tremor,dry mouth	-macrolides and azole antifungals may increase Citalopram levels -Much less dry mouth than TCAs -Sertraline decreases diazepam clearance by 32%
Paroxetine (Paxil,G) 0+..... Sertraline(Zoloft,G) 0+..... Vortioxetine (Brintellix) 0-1+……	...Nausea, sedation, dry mouth,dizziness ...Insomnia, dizziness, HA, tremor, dry mouth, GI …ALL SSRIs CAUSE BRUXISM!!	- Fluvoxamine increases BZDP levels,best TO AVOID COMBINATION. -Limit tramadol dosage due to possible serotonin syndrome
ALPHA-2 RECEPTOR ANTAGONIST		
Mirtazapine (Remeron,G) 2+……	Drowsiness, dizziness, weight gain NO BRUXISM REPORTED	BZDPs increase psychomotor impairment Minimal dry mouth, Minimal SSRI-type side effects Sedation and weight gain are problems
SEROTONIN 5HT1A SELECTIVE AGONIST		
Gepirone (Exxua) 1+ …….	..dizziness, nausea, HA, sedation, insomnia	CYP3A4 inhibitors increase levels Serotonin syndrome risk with MAOIs and Serotonergic drugs like tramadol
AMINOKETONE ANTIDEPRESSANTS		
Bupropion (Wellbutrin, Zyban,G) 2+…….	Seizures, agitation, insomnia, dry mouth	-lowest risk of sexual dysfunction of all antidepressant groups
Bupropion/DextroMethorphan 2+……	Dizziness, HA, diarrhea,somnolence,dry mouth,	-seizure risk above 300mg/day
LITHIUM		
Lithium Carbonate (Eskalith, Lithane, Lithonate, G)	Tremor, GI, thirst, polyuria, edema, taste disturbances, abnormal facial movements	-Lithium levels are increased by NSAIDs Ibuprofen, Naproxen, and Piroxicam. Best to use Diflunisal or Sulindac
MONOAMINE OXIDASE INHIBITORS (MAOIs)		
Isocarboxazid (Marplan) 2+ Phenelzine (Nardil,G) 2+ Selegiline Transdermal (Emsam) 1-2+ Tranylcypromine (Parnate,G) 2+	Orthostatic hypotension, tachycardia, HA, restlessness,insomnia, dizziness, overstimulation including increased anxiety, agitation, and manic symptoms, dry mouth, Paresthesias, diarrhea ASK ABOUT DIETARY RESTRICTIONS	-Limit total epi dose to 0.04mg in MAOI patients and aspirate repeatedly -AVOID Meperidine and Fentanyl -AVOID decongestants (Sudafed, PPA) and amphetamines -Record baseline and post-treatment BP

Table B-2
ANTI-ANXIETY MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
BENZODIAZEPINES (BZDPs)		
Alprazolam (Xanax,G) Chlordiazepoxide (Librium, G) Clorazepate (Tranxene, G) Diazepam (Valium, G) Estazolam (ProSom) Lorazepam (Ativan, G) Oxazepam (Serax, G) Temazepam (Restoril, G) Triazolam (Halcion,G)	Drowsiness, ataxia, rebound insomnia, withdrawal symptoms (difficult with Alprazolam), dizziness	-CNS depressants are additive with BZDPs -BZDP effects increased by Erythromycin, Ketoconazole, OCs, Cimetidine, Propranolol, Metoprolol
OTHER ANTI-ANXIETY AGENTS		
Buspirone (Buspar,G).....……	...Dizziness, nausea, HA, nervousness	-Xerostomia can be very pronounced
Diphenhydramine (Benadryl, G).....…	...Dry mouth, sedation, tachycardia	-CNS depressants are additive
Eszopiclone (Lunesta,g)……..	…HA, unpleasant taste, drowsiness	-Macrolides, azole antifungals and doxycycline increase Lunesta levels
Hydroxyzine (Atarax, Vistaril, G)...……	...Dry mouth, sedation, tachycardia	-Atropine potentiates anticholinergic effects of antihistamines
Ramelteon (Rozerem)…….....	...dizziness, HA, sonmolence	
Suvorexant (Belsomra)……..	…somnolence,dizziness,C-IV	-Macrolides and azole antifungals increase Sonata and Rozerem levels
Zaleplon (Sonata,g)……	…Dizziness, blurred vision, fatigue	
Zolpidem (Ambien,g,Intermezzo)……	...HA, sedation, myalgia, nausea	

Table B-3
ANTIPSYCHOTIC MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
PHENOTHIAZINES: ALIPHATIC		
Chlorpromazine (Thorazine, G) 2+ Promazine (Sparine) 3+	Drowsiness, dry mouth, orthostatic hypotension, movement disorders that can be both reversible and irreversible (tardive dyskinesia)	-CNS depressants potentiate these drugs in all cases, meperidine is worst -Epi effect decreased by alpha blockade
PHENOTHIAZINES: PIPERIDINE		
Mesoridazine (Serentil) 3+ Thioridazine (Mellaril, G) 3+	Drowsiness, dry mouth, orthostatic hypotension, movement disorders	-Same as above
PHENOTHIAZINES: PIPERAZINE		
Fluphenazine (Prolixin,Permitil,G) 1+ Perphenazine (Trilafon, G) 1+ Prochlorperazine (Compazine, G) 1+ Trifluoperazine (Stelazine, G) 1+	-Same as above except little or no interaction with epi	
PHENOTHIAZINES: THIOXANTHENES		
Thiothixene (Navane, G) 1+	Movement disorders, dry mouth, drowsiness	-Llittle or no interaction with epi
BUTYROPHENONE		
Haloperidol (Haldol, G) 1+	Movement disorders, orthostatic hypotension, tardive dyskinesia	-Same as above except little or no interaction with epi
ATYPICAL OR SECOND GENERATION		
Aripiprazole (Abilify) 0-1+ Asenapine (Saphris) 1+ Brexpiprazole (Rexulti) 1+ Carprazine (Vraylar) 1+ Clozapine (Clozaril, G) 3+ Iloperidone (Fanapt) 0-1+ Lumateperone (Caplyta) 1+ Lurasidone (Latuda) 1+ Olanzepine (Zyprexa,G) 2+ Olanzepine/samidorphan (Lybalvi) Paliperidone (Invega) 0-1+ Pimozide (Orap) 2+ Quetiapine (Seroquel,G) 0-1+ Risperidone (Risperdal,G) 0-1+ Ziprasidone (Geodon,G) 1+	..HA,agitation, anxiety, insomnia, weight gain ...sedation, EPS, loss of oral sensation …weight gain, CYP450 interactions …sedation,CYP450 interactions ..Drowsiness, dizziness, salivation, dry mouth, aplastic anemia 1.3%, …dizziness,sedation,weight gain …sedation, HA, dry mouth, dizziness …nausea, sedation, movement disorders ..Weight gain, sedation good for refractory -Samidorphan is an opioid antagonist ..QT prolongation,lower risk of weight gain ..Movement disorders, drowsiness,dry mouth ..HA, drowsiness, dizziness ..HA, insomnia,agitation, weight gain, EPS ..HA, drowsiness, dizziness, weight gain	-Asenapine intx with fluoroquinolones -Clozapine with BZDP can produce resp. depression and hypotension -Lorazepam levels incr. by Quetiapine -Macrolides and azole antifungals intx with aripiprazole, iloperidone, lurasidone, pimozide and Quetiapine-increase antipsychotic levels -Clozapine may reduce effects of codeine, hydrocodone, oxycodone, tramadol -Avoid mod-strong CYP3A4 inhibitors with Caplyta (includes clarithromycin, ciprofloxacin, fluconazole) AVOID OPIOIDS WITH LYBALVI
MUSCARINIC AGONIST COMBO Xanomeline/trospium (Cobenfy)	NAUSEA, dyspepsia, constipation, vomiting, hypertension, tachycardia, GERD	Urinary retention may be serious. Risk of orofacial angioedema. 2D6 inhibitors

Table B-4
ANTICONVULSANT MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
Carbamazepine (Tegretol, Carbatrol, G).....	...Drowsiness, ataxia, severe blood dyscrasias	-CNS depressants will potentiate all drugs in this category -Possible bleeding with Valproate -Gingival overgrowth with Phenytoin -Erythromycin and propoxyphene increase Carbamazepine levels -Erythromycin increases Depakene levels -Low stress environment-consider sedative premedication (BZDP) -Take seizure control history often -Aspirin increases Depakene levels -Carbamazepine increases APAP liver toxicity, decreases APAP effect -Phenytoin may increase meperidine toxicity and decrease its effectiveness
Clonazepam (Klonopin, G).....	...Drowsiness, ataxia, behavior disorders	
Felbamate (Felbatol,G)……..	…Aplastic anemia, liver failure, HA	
Gabapentin (Neurontin,G).....	...Dizziness, ataxia, fatigue, nystagmus	
Lamotrigine (Lamictal,G).....	...Dizziness, ataxia, HA, diplopia, rash	
Levetiracetam (Keppra,G)…….	…Drowsiness, dizziness	
Oxcarbazepine (Trileptal)……..	…Drowsiness, ataxia	
Phenobarbital (G).....	...Sedation, behavior disorders	
Pregabalin (Lyrica,G)…….	…Drowsiness, dry mouth, peripheral edema	
Phenytoin (Dilantin, G).....	...Drowsiness, ataxia, gingival hyperplasia	
Sodium Valproate(Depakene, Depakote, G).	...GI, HA, ataxia, drowsiness, tremor, thrombocytopenia	
Tiagabine (Gabitril,G)…….	…dizziness, HA, tremor, nervousness	
Topiramate (Topamax,G)……	...Drowsiness, dizziness, fatigue	
Zonisamide (Zonegran)…….	…Drowsiness, dizziness, nausea	

Table B-5
ANTIPARKINSON'S DISEASE MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
DOPAMINERGIC AGENTS		
Amantadine (Symmetrel, G).....	...Nausea, Dizziness, insomnia, dry mouth	-Levodopa can increase effects of epi -Patient management is difficult due to movements and excess saliva -Macrolides increase Ropinirole
Bromocriptine (Parlodel).....	...Nausea, abnormal movements, dizziness, drowsiness	
Carbidopa/Levodopa (Sinemet/CR, G).....	...Movement disorders, GI, altered taste, excessive salivation, bruxism	
Pergolide (Permax).....	...Nausea, abnormal movements, sedation, rhinitis	
Pramipexole (Mirapex)……	…hallucinations,nausea, dizziness, sedation, sudden sleep attacks	
Ropinirole (Requip,G)…….	…syncope, nausea, dissiness, sedation	
ANTICHOLINERGICS		
Benztropine (Cogentin, G) Biperiden (Akineton) Trihexyphenidyl (Artane, G)	Drowsiness, dry mouth, tachycardia, confusion	-Xerostomia can be severe -CNS depressants have additive effect -Confusion is common
MISCELLANEOUS PARKINSON'S DISEASE AGENTS		
Rasagiline (Azilect,g)……	…arthralgias, depression, dyspepsia, falls	-rasagiline is a MAOI (type B) inhibitor so avoid antidepressants, cyclobenzaprine, dextromethorphan, fluoroquinolones, meperidine, pseudoephedrine. Limit epi dose to 0.04mg per 2 hour dental visit. -Selegiline is a MAOI (type B) so avoid Meperidine, limit total epi dose to 0.04mg until this interaction is investigated -Limit epi with Comtan or Ongentys
Safinamide (Xadago)…….	…..dyskinesias, falls, nausea, insomnia	
Selegiline (Eldepryl,G).....	...Nausea, dizziness, confusion, dry mouth	
Entacapone (Comtan,G)……	…diarrhea, avoid sudden d/c	
Tolcapone (Tasmar)	….hepatic toxicity limits use	
Opicapone (Ongentys)…….	…dyskinesia, hypotension,avoid sudden d/c	

Table B-6
ADD/ADHD MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
CNS STIMULANTS		
Amphetamine mixtures (Adderall,G) Methylphenidate (Concerta, Metadate CR/ED, Ritalin, Ritalin-SR, G) Dexmethylphenidate (Focalin, G)	Amphet-dry mouth dyskinetic movements, increased BP, pulse May cause seizures, nervousness, insomnia, dizziness, HA, dyskinesia, tachycardia, anorexia	1. Meth, Amphet and Dex interact with MAOIs and furazolidine 2. Dex and Amphet interact with TCAs-decreased dex or amphet effects 3. Low stress environment 4. Monitor BP and pulse 5. Possible caries increased 6. Qelbree is a SNRI non-stimulant
Dextroamphetamine (Dexedrine, G)	Dex- dry mouth, dysgeusia, no seizure increase	
Lisdexamfetamine (Vyvanse)	Prodrug of dextroamphetamine-less abuse potential but still Schedule II CS	
Viloxazine (Qelbree)…….	Increased BP & HR, somnolence, NV	

Table C-1
SEX HORMONES

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
ORAL CONTRACEPTIVES (Combination or Triphasic are Most Commonly Prescribed)		
(Lo-Ovral, Ortho Novum, Brevicon, Modicon, Norinyl, Genora, Tri-levlen, etc.) Seasonale is a combination OC with only four menstrual periods per year	…Nausea, HA, edema, weight gain, intraoral soft tissue changes (gingivitis) [*if dental antibiotics are taken for 48 hours or more, advise additional barrier contraception for the remainder of the pill pak.*]	-Progestin causes increased inflammatory response to plaque -Increased dry socket for 21/28 days -BZDP will have longer activity with OCs -Oral mucosa is more resistant to trauma
HORMONE REPLACEMENT THERAPY (HRT)		
Conjugated Estrogens, equine (Premarin, G) Conjugated Estrogens, synthetic (Cenestin) Esterified Estrogens (Estratab, Menest) Estradiol (Estrace) transdermal (Alora, Climara, Estraderm, Fem Patch, Vivelle-Dot)	Edema, HA, melasma, nausea, increased risk of thromboembolic episode	-Oral mucosa is more resistant to ulcerationBone density is increased -BLACK BOX WARNING FOR POSSIBLE INCREASED RISK OF CARDIAC AND THROMBOEMBOLIC EVENTS

Table C-2
ORAL and NON-ANTIDIABETIC MEDICATIONS –

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
BIGUANIDES		
Metformin (Glucophage, G) …… Metformin/glipizide (Metaglip) …… Metformin/glyburide (Glucovance) …….. Metformin/pioglitazone (Actoplus Met) ……. Metformin/rosiglitazone (Avandamet) ……	-Diarrhea,bloating, Vit B-12 malabsorp, taste -Hypoglycemia, GI -Hypoglycemia, GI -GI, URI, HA, sinusitis, bloating, taste -GI, URI, HA, edema, bloating, taste disturb. -Hypoglycemia, HA	- Metformin with prednisone may cause lactic acidosis -possible hypoglycemia with Metaglip and Glucovance combination drugs -Metformin is first line therapy -No risk of hypoglycemia as a single agent
SECOND GENERATION SULFONYLUREAS ("GL" for Glucose Reduction)		
Glimepride (Amaryl, g) Glipizide (Glucotrol,XL,G) Glyburide Micronase,Glynase PresTab, G)	Hypoglycemia, GI, weight gain	-NSAIDs and high-dose Salicylates (aspirin) increase hypoglycemia with all agents -Precautions about preventing hypoglycemia
ALPHA-GLUCOSIDASE INHIBITORS		
Acarbose (Precose) Miglitol (Glyset)	GI, flatulence, diarrhea Flatulence, diarrhea	-no hypoglycemia as single agents
THIAZOLIDINEDIONES ("GLITAZONES")		
Pioglitazone (Actos,G) Rosiglitazone (Avandia)	URI, HA, sinusitis URI, HA, edema	-macrolides and azole antifungals inc. levels -no hypoglycemia as single agent
DPP-4 INHIBITORS ("GLIPTINS")	**Incretin Enhancers**	
Alogliptin (Nesina)…… Linagliptin (Tradjenta)……. Saxagliptin (Onglyza)…… Sitagliptin (Januvia) ……..	-nasopharyngitis, HA,URI -hypoglycemia, nasopharyngitis, GI -hypoglycemia, HA, peripheral edema -hypoglycemia, GI	-acute pancreatitis and hepatic toxicity have been seen with all DPP-4 inhibitors -DPP-4 inhibitors may cause hypersensitivity reactions including rash and angioedema
GLP-1 AGONISTS ("GLUTIDES")	**Incretin Mimetics**	**Only one "glutide" is orally available***
Dulaglutide (Trulicity)..... Exenatide (Byetta,Bydureon) ..... Liraglutide (Victoza)..... Lixisenatide (Adlyxin)..... Semaglutide oral* (Rybelsus)..... Semaglutide inj (Ozempic,Wegovy-weight loss indication only).....	-low risk of hypoglycemia -acute pancreatitis, nausea, hypoglycemia -possible thyroid C-cell tumor risk, GI,HA -GI, HA, dizziness, -possible thyroid C-cell tumor risk,GI,HA -possible thyroid C-cell tumor risk,GI,HA -increased risk of vomiting with high doses	-All reduce APAP levels so give APAP 1 hour prior to injection; Also, Give oral antibiotics 1 hour prior to either injection -All agents have low risk of hypoglycemia -All agents cause weight loss -INCREASED RISK OF ASPIRATION DURING GENERAL ANESTHESIA-recommend skipping dose 1 week prior to surgery
GLP-1 & GIP AGONIST ("Twincretin" Tirzepatide (Mounjaro injection).....	-best weight loss of all diabetes drugs -GI,possible thyroid C-cell tumor	-reduced OC absorption -AVOID dehydration
SGLT2 INHIBITORS ("FLOZINS")		
Bexagliflozin (Brenzavvy)..... Canagliflozin (Invokana)..... Dapagliflozin (Farxiga)..... Empagliflozin (Jardiance)..... Ertugliflozin (Steglatro).....	-Increased risk of genital yeast infection -may increase risk of stroke -may increase risk of bladder cancer -may increase risk of UTI -	-All cause weight loss and decreased BP -Low risk of hypoglycemia -CV benefit-can,dap,empag,ertug -Kidney benefit-can, dap, empag -All increase risk of UTI and genital yeast

Recommendation 1	Standardized preoperative assessment for risk of delayed gastric emptying (yes/no): 1. Presence of gastrointestinal symptoms suggesting delayed gastric emptying; recent dose increases, higher doses, and weekly administered medications may increase the risk of gastrointestinal symptoms 2. Medical conditions beyond GLP-1RA usage, which may also delay gastric emptying
Recommendation 2	Selective preoperative care plan based on delayed gastric emptying assessment and shared decision-making: 1. Continue GLP-1RA therapy preoperatively if there is no concern for delayed gastric emptying 2. If elevated risk of delayed gastric emptying exists: a. Recommend liquid only diet for at least 24 h before procedure with usual recommended fasting protocol, or b. Evaluation of the feasibility of medication bridging if GLP-1RAs need to be discontinued
Recommendation 3	On the day of procedure, reassess for delayed gastric emptying and mitigate risk if clinical concern: 1. Proceed with procedure as planned if there is no concern for delayed gastric emptying 2. If elevated risk of delayed gastric emptying exists: a. Consider point-of-care gastric ultrasound and/or b. Consider rapid sequence induction of general anesthesia, if appropriate c. Minimize procedure cancellation when possible

GLP-1RA, glucagon-like peptide-1 receptor agonist.

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Table C-3
INSULINS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
RAPID AND SHORT-ACTING		
Humalog,Novolog,Apidra – rapid acting **Humulin R,Novolin R – short acting regular**	**-onset 15-30 minutes, duration 3-5 hours** **-onset 30-60minutes, duration 6-10 hours**	**-peak effect 30min to 1 hour** **-peak effect 1-4 hours**
INTERMEDIATE ACTING		
Humulin N, Novolin N (i.e. NPH)	**-onset 1-2 hours** **-duration is up to 24 hours**	**-peak effect 6-14 hours** **-peak effect 4-12 hours**
LONG-ACTING		
Lantus (insulin glargine) **Levemir (insulin detemir)**	**-onset 1.1 hours, duration 24 hours** **-onset 1.1-2 hours, duration 24 hours**	**-NO SIGNIFICANT PEAK** **-NO SIGNIFICANT PEAK**

Table C-4
CORTICOSTEROID MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
SHORT-ACTING		
Hydrocortisone (Cortef, G)	**Fluid retention (can be significant), insomnia, weight gain, adrenal suppression, increased risk of infection, poor wound healing, hypertension, K+ loss, osteoporosis, peptic ulcer formation, growth suppression in children, increased friability of oral soft tissue** **Diabetes may be unmasked and predominant patient mood will be intensified. Insomnia, nervousness, tachycardia and tremor can be seen with moderate to high daily doses.**	**-"Window of vulnerability" is hydrocortisone 20mg-60mg daily or prednisone 5-15mg/day for greater than 21 continuous days.** **Additional steroids may be needed to supplement the adrenal suppressed patient during acute periods of stress** **-Take extra precautions against viral, bacterial or fungal infection** **-Avoid Salicylates such as aspirin**
INTERMEDIATE-ACTING		
Prednisone (Deltasone, G) **Prednisolone (Delta-Cortef, G)** **Triamcinolone (Kenalog, G)** **Methylprednisolone (Medrol, G)**	**Same as above, but fluid retention only with high doses of these synthetic agents**	**-Same as above** **-Erythromycin inhibits metabolism of Methylprednisolone**
LONG-ACTING		
Dexamethasone (Decadron, G) **Betamethasone (Celestone, G)**	**Same as above, but fluid retention only with high doses of these synthetic agents**	**-dexamethasone induces CYP2D6 so enhances codeine and hydrocodone-** **acute perioperative use in oral surgery doesn't increase post-op complications**

Table C-5

OSTEOPOROSIS MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
Calcitonin-salmon nasal spray (Miacalcin)	Rhinitis, nausea, salty taste, dry mouth	-local irritation or oropharynx is possible
BISPHOSPHONATES (oral and/or injectable) -Alendronate (Fosamax oral,G-daily,weekly) -Ibandronate (Boniva ,G-also by injection q 3mo but injection is not generic yet) -Pamidronate (Aredia) – injection only -Risedronate (Actonel oral -daily, weekly) -Zoledronic Acid (Zometa, Reclast)-injection only-once yearly for osteoporosis is Reclast	Pain, GI, HA,possibility of osteonecrosis of the jaw (ONJ), Zometa and Aredia are injectable bisphosphonates for cancer chemo hypercalcemia with much higher risk of ONJ than oral agents. Reclast is a once yearly dose of zoledronic acid and is also associated with increased risk of ONJ post alveolar bone trauma.	Must be taken with 8oz. of water first thing in the AM. No other medications within 30 minutes of all "dronates". ONJ- Minimize trauma, possibly avoid implants, early recognition of painful extraction site lesions, AVOID DEBRIDEMENT!!! -Print patient information sheet from the ADA website "For the Dental Patient" under the title "Bisphosphonate Medications"
RANKL INHIBITOR		
-Denosumab (Prolia Injection)……	..Likely to have same risk of ONJ!	..Indicates intolerance to bisphosphonates
BONE-BUILDING INJECTABLE MEDICATIONS		
Abaloparatide (Tymlos)……. Teriparatide (Forteo)…….. Romosozumab (Evenity)……..	..Orthostatic hypotension, dizziness ..HA, dizziness,nausea, injection site ..Arthralgia, HA, black box for MI	-Increased risk of osteosarcoma in rats using 3-20x human dosages, increased serum calcium -Osteonecrosis of the Jaw is a risk with Evenity

Table D RESPIRATORY SYSTEM MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
ANTIHISTAMINES		
Azatadine (Optimine, Trinalin) Azelastine (inhaled) (Astelin,G) Brompheniramine (Dimetane, G) Carbinoxamine (Clistin) Cetirizine (Zyrtec, OTC, G) Chlorpheniramine (Chlor-Trimeton, G) Clemastine (Tavist, G) Cyproheptadine (Periactin, G) Desloratidine (Clarinex,G) Diphenhydramine (Benadryl, G) Fexofenadine (Allegra, Allegra OTC,G) Hydroxyzine (Atarax, Vistaril, G) Loratidine (Claritin, G, OTC) Triprolidine (Actifed, G)	Drowsiness, dry mouth, palpitations, thickening of bronchial secretions with traditional antihistamines such as chlorpheniramine,diphenhydramine, hydroxyzine and triprolidine (Cetirizine, Fexofenadine and Loratidine have limited anticholinergic side effects.)	-Dry mouth can be significant with diphenhydramine and hydroxyzine -CNS depressants have additive effects with diphenhydramine and hydroxyzine -Oral lesions with Triprolidine
SYMPATHOMIMETIC BRONCHODILATORS		
<u>INHALERS</u> Albuterol (Proventil, Ventolin, G)-SABA Arformoterol (Brovana) - LABA Bitolterol (Tornalate)-SABA Formoterol (Foradil) - LABA Levalbuterol (Xopenex)-SABA Metaproterenol (Metaprel, Alupent, G)-SABA Olodaterol (Striverdi) - LABA Pirbuterol (Maxair)-SABA Salmeterol (Serevent,Advair Diskus) - LABA Terbutaline (Brethaire)-SABA	Tremor, tachycardia, bad taste, oral irritation -long acting (LA) beta agonist for COPD and can exacerbate acute bronchospasm during an asthma attack Headache due to its long action	-Inhaler use just prior to dental treatment may prevent asthma during the appointment. (Don't use LA beta agonist inhaler or corticosteroid inhaler.) -Dental office should have Albuterol inhaler available for patients -Rinse mouth and throat after use to prevent local adverse effects.
XANTHINE BRONCHODILATORS		
Theophylline Bead-filled caps (Slo-Bid, Slo-Phylline, etc.) Theophylline SR tablets (Theolair-SR, etc.)	Nausea, HA, tachycardia, insomnia, tremor, irritability because caffeine derivative	-Used mostly as chronic medication -Ketoconazole decreases Theophylline -Macrolides increases Theophylline
CORTICOSTEROID RESPIRATORY AGENTS-Inhaled Corticosteroids (ICS)		
<u>INHALERS-ICS</u> Beclomethasone (Vanceril, Vancenase/AQ DS, Beclovent, Beconase/AQ) Budesonide (Rhinocort, Pulmicort,g) Flunisolide (AeroBid, Nasalide, Naserel) Fluticasone (Flonase, Flovent,Advair Diskus) Triamcinolone (Azmacort, Nasacort/AQ)	Soft palate irritation, atrophic candida on the soft palate or buccal mucosa SYMBICORT is Formoterol/budesonide ADVAIR DISKUS is Salmeterol/fluticasone	-Check often for palatal candida infection -Recommend rinsing or an inhaler adapter to prevent atrophic candida -Rinse with water after each use. -Chronic ICS use increases pneumonia risk in patients with severe COPD.

LABA/ICS COMBINATION INHALERS	**BREO ELLIPTA is Vilanterol/fluticasone**	
Mast Cell Migration Inhibitor Inhalers **Cromolyn (Intal, Nasalcrom)** **Ipratropium (Atrovent)** **Nedocromil (Tilade)** **SABA/Mast Cell Inhibitor COMBO inhaler**	**…dry oropharynx, cough** **COMBIVENT is Albuterol/ipratropium**	**All are for chronic therapy** **Ipratropium is indicated for BOTH asthma and COPD** **Ipratropium is short-term therapy for rhinitis in 5yo and up age groups**
Long-Acting Muscarinic Antagonists (LAMAs)		
Aclidinium (Tudorza) **Glycopyrrolate (Lonhala)** **Revefenacin (Yupelri)** **Tiotropium (Spiriva)** **Umeclidinium (Incruse)** **LABA/LAMA Combo inhalers** **ICS/LAMA/LABA Combo inhalers**	**...dry oropharynx** **...dry oropharynx** **…dry oropharynx** **...dry oropharynx** **…dry oropharynx** **ANORO is Vilanerol/Umeclidinium** **TRELEGY Fluticasone/Umeclidinium/Vilanterol**	**-All of these are for chronic daily use only and should NOT be used "as needed" for acute exacerbations of symptoms.** **-Chronic ICS use increases pneumonia risk in patients with severe COPD.** **-Rinse after use to reduce dry mouth sx.**
LEUKOTRIENE RECEPTOR ANTAGONISTS		
Montelukast (Singulair,G) **Zafirlukast (Accolate)**	**-HA, pharyngitis, cough** **-HA, lethargy, rare vasculitis**	**-Phenobarb dec. montelukast levels** **-Zafirlukast levels dec. by 40%** **macrolides & inc by 45% with ASA**

Table E
GASTROINTESTINAL MEDICATIONS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
ANTICHOLINERGICS/ANTISPASMODICS		
Clidinium Br (Quarzan) **Dicyclomine (Bentyl, G)** **Glycopyrrolate (Robinul)** **Oxybutynin (Ditropan)** **Propantheline Br (Pro-Banthine, G)**	**Dry mouth, altered taste, dysphagia, palpitations, drowsiness, excitement**	**-Dry mouth can be very significant** **-CNS drugs can have additive effects** **-Some are used to decrease saliva flow during dental visits**
H_2 ANTAGONISTS		
Cimetidine (Tagamet,HB=OTC,G) **Famotidine (Mylanta AR, Pepcid,AC=OTC, ZANTAC IS NOW FAMOTIDINE AS WELL!)** **Nizatidine (Axid,AC=OTC)**	**HA, fatigue, thrombocytopenia, rarely erythema multiforme**	**-Cimetidine decreases clearance of BZDPs, Lidocaine, Carbamazepine, Metronidazole** **-All H_2 agents decrease absorption of Ketoconazole, but not Fluconazole**
PROSTAGLANDIN E-2 ANALOGUE		
MISOPROSTOL (Cytotec)	**Abortifacient, diarrhea**	**-Patient at high risk for GI ulcers so avoid aspirin and NSAIDs**
PROTON PUMP INHIBITORS		
Dexlansoprazole (Dexilant)……. **Esomeprazole (Nexium)……..** **Lansoprazole (Prevacid,G)……** **Omeprazole (Prilosec, G, OTC)……** **Pantoprazole (Protonix)…….** **Rabeprazole (Aciphex)…….**	**Diarrhea, abdominal pain, nausea** **HA, GI including diarrhea** **HA, GI including diarrhea** **HA, GI, myalgias** **HA, GI, hyperglycemia** **HA, dizziness, infection**	**-BZDP levels increased,fluconazole increases dexlansoprazole levels** **-Clarithromycin increases omeprazole** **-Omeprazole & rabeprazole increase half-life of diazepam and triazolam** **-All decrease Ca, Mg, B12 absorption**
GASTROINTESTINAL PROKINETIC AGENTS		
Metoclopramide (Reglan,G).....	**..Fatigue,drowsiness,movement disorders** **..HA, diarrhea, abdominal pain**	**-Narcotics antagonize metoclopramide** **-CNS depressants can add to drowsiness with Metoclopramide**

Table F
IMMUNOMODULATORS AND BIOLOGICS FOR AUTOIMMUNE DISORDERS

CATEGORY	ADVERSE EFFECTS	TREATMENT IMPACT
HYDROXYCHLOROQUINE **(Plaquenil, G)**	**Eye toxicity, oral lichenoid lesions,** **pigmentation or oral mucosa**	**Oral melanosis or ulcerative lesions**

SULFASALAZINE (Azulfidine, G)	**GI, HA, fever, blood dyscrasias**	**-Antibiotics may interfere with effects**
TUMOR NECROSIS FACTOR INHIBITORS, JAK INHIBITORS AND BIOLOGICS		
Abatacept (Orencia) T cell inhibitor……	**..Anemia, infectious disease, HA**	**-false elevation of finger stick glucose**
Adalimumab (Humira) TNFi……	**..URI, UTI, oral thrush, ulcerative stomatitis**	**-All drugs in this category cause oral ulcerations and increased infections**
Anakinra (Kineret) IL-1 inhibitor……..	**..injection site rx, URI, HA, nausea**	
Apremilast (Otezla) – PDE-4 Inhibitor…	**..Depression,diarrhea, nausea, HA**	**-Compromised host defense mechanisms indicate need to minimize infection risk**
Azathioprine(Azasan,Imuran,g).....	**..Neutropenia, URI, UTI, Oral Thrush**	
Baricitinib (Olumiant) JAK Inhibitor…..	**...Nausea, vomiting, bone marrow suppression**	**-Cyclosporine gingival overgrowth is dose related and occurs in 5-16%**
Certilizumab (Cimzia) TNFi……..	**…URI,UTI, arthralgia,rash,increased CA risk?**	**-Cyclosporine levels increased with Erythro, Ketoconazole, Fluconazole**
Cyclophosphamide (Cytoxan,g).....	**...Alopecia, bone marrow suppression, sterility**	**-NSAIDs increase renal toxicity of Cyclosporine**
Cyclosporine (Sandimmune, Neoral,g).....	**Renal dysfunction, hypertension, hirsutism, tremor, gingival overgrowth**	
Etanercept (Enbrel) TNFi …….	**…URI, HA, other infections, increase CA risk?**	
Golimumab (Simponi) TNFi…….	**…URI,Herpes, blood dyscrasias**	
Infliximab (Remicade) TNFi.....	**…URI, UTI, Oral Thrush, increased cancers**	
Leflunomide (Arava)……	**…diarrhea, alopecia, URI**	**-NSAID levels increased by Arava**
Methotrexate (Rheumatrex, G).....	**...GI ulceration, bone marrow suppression**	**-30% rate or oral ulcers with methotrexate chronic therapy**
Rituximab (Rituxan) B cell depleter	**…URI, nasopharyngitis, bronchitis**	**-NSAIDs increase Methotrexate levels**
Secukinumab (Cosentyx) IL-17A blocker	**…URI,candida, herpes, neutropenia**	**-Neutropenia in up to 10% of patients with Sarilumab**
Sarilumab (Kevzara) IL-6 antagonist…..	**…Diverticulitis,serious infection risk**	
Tacrolimus (Prograf,G) calcineurin inhibitor…	**…CNS Stimulation, Renal Dysfunction, blood dyscrasias, metabolic disorders**	**-Macrolides and azole antifungals may increase tacrolimus levels**
Tocilizumab (Actemra) IL-6 inhibitor	**…URI,nasopharyngitis,HA,hypertension**	**Stop Xeljanz 7 days prior to surgery**
Tofacitinib (Xeljanz) JAK inhibitor	**…lymphomas,hepatic and blood toxicity**	**Avoid fluconazole with Xeljanz**
Upadacitinib (Rinvoq) JAK Inhibitor	**…Thrombosis risk, blood toxicity**	**Avoid live vaccines with Stelara**
Ustekinumab (Stelara)IL12&23 blocker	**…sinus infections, malignancies**	**Avoid live vaccines with JAK inhibitors**

Narrative Review

Emerging antiresorptive medications and their potential implications for dental surgeries

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Practical Implications. **Patients who received antiresorptive therapy for malignancy were at higher risk of developing MRONJ than those who received the therapy for osteoporosis, regardless of the route of administration and type of drug. Antiangiogenic agents, bevacizumab, aflibercept, and tyrosine kinase inhibitors such as sunitinib were implicated most commonly in the development of MRONJ. Patients who are taking multiple doses of angiogenic inhibitors should be monitored closely for early diagnosis of possible MRONJ.**

Key Words. Angiogenesis inhibitors; antiangiogenic agents; antiresorptive agents; bisphosphonates; denosumab; dental surgery; medication-related osteonecrosis; monoclonal antibody; osteonecrosis.

Table 3. Commercially available antiresorptive medications in the United States (not including bisphosphonates).

GENERIC NAME	TRADE NAME (MANUFACTURER)	ROUTE OF ADMINISTRATION	MECHANISM OF ACTION*	INDICATION FOR USE
Aflibercept	Eylea (Regeneron Pharmaceuticals)	Intravitreal injection	A soluble decoy receptor that binds VEGF A and placental growth factor	Neovascular AMD, macular edema, diabetic retinopathy
Bevacizumab	Avastin (Genentech)	IV‡‡ injection or infusion	Inhibits VEGF binding	CRC, NSCLC, KCC, breast cancer, ovarian cancer, cervical cancer, glioblastomas, neovascular AMD††
Cabozantinib†	Carbometyx (Exelixis), Cometriq (Exelixis)	Oral	Tyrosine kinase inhibitor specific to VEGF§§ 2	Medullary thyroid cancer, KCC,‡ hepatocellular cancer
Denosumab	Prolia (Amgen)	Subcutaneous injection	Inhibits the receptor activator of nuclear factor κB ligand	Osteoporosis
	Xgeva (Amgen)	Subcutaneous injection	Inhibits the receptor activator of nuclear factor κB ligand	Prevention of skeletal-related events in patients with multiple myeloma or bone metastases from solid tumors
Everolimus	Afinitor (Novartis)	Oral	Inhibits the mammalian target of rapamycin	KCC, subependymal giant cell astrocytoma, NET, breast cancer
	Zortress (Novartis)	Oral	Inhibits the mammalian target of rapamycin	Kidney transplant rejection prophylaxis, NET
Lenvatinib†	Lenvima (Eisai)	Oral	Tyrosine kinase inhibitor specific to VEGF 2	Progressive, radioactive iodine-refractory differentiated thyroid cancer, KCC, hepatocellular cancer, endometrial cancer
Lorlatinib†	Lorena (Eisai)	Oral	Tyrosine kinase inhibitor specific to VEGF 2	NSCLC§
Pazopanib†	Votrient (GlaxoSmithKline)	Oral	Tyrosine kinase inhibitor specific to VEGF 2	KCC, soft-tissue sarcoma, GIST{
Ramucirumab†	Cyramza (Eli Lilly)	IV injection or infusion	Inhibits VEGF binding	Gastric cancer or gastroesophageal junction adenocarcinoma, NSCLC, CRC, hepatocellular cancer
Ranibizumab†	Lucentis (Genentech)	Intravitreal injection	A soluble decoy receptor that binds VEGF A and placental growth factor	Neovascular AMD, macular edema, diabetic retinopathy, myopic choroidal neovascularization
Regorafenib†	Stivarga (Bayer Pharmaceuticals)	Oral	Tyrosine kinase inhibitor specific to VEGF 2	CRC,# GIST, hepatocellular cancer
Sirolimus†	Rapamune (Wyeth Pharmaceuticals)	Oral	Inhibits the mammalian target of rapamycin	Kidney transplant rejection prophylaxis, lymphangioleiomyomatosis
Sorafenib†	Nexavar (Bayer Pharmaceuticals)	Oral	Tyrosine kinase inhibitor specific to VEGF 2	KCC, hepatocellular cancer, thyroid cancer
Sunitinib	Sutent (Pfizer)	Oral	Tyrosine kinase inhibitor specific to VEGF 2	KCC, GIST, pancreatic NET**
Temsirolimus†	Torisel (Wyeth Pharmaceuticals)	IV infusion	Inhibits the mammalian target of rapamycin	KCC
Vandetanib†	Caprelsa (AstraZenica Pharmaceuticals)	Oral	Tyrosine kinase inhibitor specific to VEGF 2	Medullary thyroid cancer

*** Vascular endothelial growth factor receptor 2, vascular endothelial growth factor, skeletal-related events, kidney cell cancer, differentiated thyroid cancer, gastrointestinal stromal tumors, pancreatic malignant neuroendocrine tumor, colorectal cancer, nonesmall cell lung cancer, ageerelated macular degeneration. † To date, no reported cases in the literature have associated this drug with medication-related osteonecrosis of the jaw. ‡ KCC: Kidney cell cancer. § NSCLC: Nonesmall cell lung cancer. { GIST: Gastrointestinal stromal tumor. # CRC: Colorectal cancer. ** NET: Neuroendocrine tumor. †† AMD: Age-related macular degeneration.**

‡‡ IV: Intravenous §§ VEGF: Vascular endothelial growth factor.

NOACS/DOACS*: PERIOPERATIVE MANAGEMENT

Thrombosis Canada
Thrombose Canada

OBJECTIVE:

To provide guidance for the perioperative management of patients who are receiving a direct oral anticoagulant (DOAC) and require an elective surgery/procedure.

For guidance on management of patients who require an urgent or emergency surgery/procedure, please refer to the Perioperative Anticoagulant Management Algorithm found on the Thrombosis Canada website under the "Tools" tab.

BACKGROUND:

Four DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) are approved for clinical use in Canada based on findings from large randomized trials.

The perioperative management of DOAC-treated patients aims to interrupt anticoagulant therapy (if necessary) so there is no (or minimal) residual anticoagulant effect at the time of surgery, and to ensure timely but careful resumption after surgery so as to not incur an increased risk for post-operative bleeding.

There are 3 important considerations for perioperative management of patients taking a DOAC:

1) Reliable laboratory tests to confirm the absence of a residual anticoagulant effect of DOACs are not widely available.
2) Half-lives of DOACs differ and increase with worsening renal function, affecting when the drug should be stopped before surgery.
3) DOACs have rapid onset of action, with a peak anticoagulant effect occurring 1-2 hours after oral intake.

In the absence of laboratory tests to reliably measure their anticoagulant effect, the perioperative administration of DOACs should be influenced by:

1) Drug elimination half-life (with normal renal function),
2) Effect of renal function on drug elimination half-life
3) Bleeding risk associated with the type of surgery/procedure and anesthesia (**Table 1**)
4) Whether patient is to receive spinal/epidural anesthesia

EVIDENCE SUPPORTING PERIOPERATIVE MANAGEMENT OF PATIENTS TAKING A DOAC:

There are emerging data relating to the efficacy and safety of the proposed perioperative management of DOAC-treated patients. In RELY, a trial comparing dabigatran (150 mg or 110 mg)

*NOACs/DOACs = Non-vitamin K antagonist Oral AntiCoagulants, also known as Direct OralAnticoagulants

with warfarin for stroke prevention in atrial fibrillation, there were >4,500 patients who had anticoagulant interruption for a surgery/procedure. The incidence of perioperative bleeding was similar in dabigatran- and warfarin-treated patients, suggesting that dabigatran-treated patients can be safely managed perioperatively. Similar findings have been observed for the perioperative management of apixaban-treated, edoxaban-treated and rivaroxaban-treated patients.

PERIOPERATIVE MANAGEMENT:

Patients Receiving Dabigatran

Pre-Operative Management (Table 2):

- **Minor surgery/procedure (LOW BLEEDING RISK):** In patients who require a minor dental procedure, cataract procedure, or minor skin procedure; it is likely safe not to interrupt anticoagulation (as is done in warfarin-treated patients) but data to support such practice is lacking. An alternative approach would be to hold dabigatran on the day of the procedure or, if dabigatran is not interrupted, to delay that day's dose for 4-6 hours after the procedure.
- **MODERATE BLEEDING RISK Procedures:** Stop dabigatran 1 day before surgery/procedure (i.e. skip 2 doses before a surgery/procedure), which corresponds to approximately 2-3 half-lives elapsed between stopping dabigatran and surgery. There may be a 12-25% anticoagulant effect at the time of surgery, which is acceptable for these procedures.
- **Major surgery/procedure including neuraxial anesthesia (HIGH BLEEDING RISK)**: Depending on renal function, stop dabigatran 2 or 4 days before surgery (i.e. skip 4 or 8 doses), which corresponds to approximately 4-5 half-lives elapsed between stopping dabigatran and surgery. This ensures minimal (3-6%) residual anticoagulant effect at the time of surgery and allows patients to have spinal anesthesia or high bleeding risk surgery (e.g. intracranial or cardiac).
- If renal function is moderately impaired (CrCl 30-49 mL/min), 1-2 additional days of interruption is required to ensure elimination of any residual anticoagulant effect, as 80% of dabigatran is cleared by the kidneys.

Post-Operative Management (Table 3):

Resumption of dabigatran 150 mg or 110 mg twice daily should be done cautiously after major surgery or in patients at increased bleeding risk, as this is a therapeutic-dose which is higher than that used for post-operative VTE prevention.

Patients Receiving Rivaroxaban

Pre-Operative Management (Table 2):

- **Minor surgery/procedure (LOW BLEEDING RISK)**: In patients who require a minor dental procedure, cataract procedure, or minor skin procedure; it is likely safe not to interrupt anticoagulation (as is done in warfarin-treated patients) but data to support such practice is lacking. An alternative approach would be to hold rivaroxaban on the day of the procedure or, if rivaroxaban is not interrupted, to delay that day's dose for 4-6 hours after the procedure.

- **MODERATE BLEEDING RISK procedure:** Stop rivaroxaban 1 day before surgery/procedure (i.e. skip 1 dose), which corresponds to approximately 2-3 half-lives elapsed between stopping rivaroxaban and surgery.
- **Major surgery/procedure including neuraxial anesthesia (HIGH BLEEDING RISK)**: Stop rivaroxaban 2 days before surgery (i.e. skip 2 doses), which corresponds to approximately 4-5 half-lives elapsed between stopping rivaroxaban and surgery.

Post-Operative Management (Table 3):

Resumption of rivaroxaban 20 mg (or 15 mg if usual dose) once daily should be done cautiously after major surgery or in patients at increased bleeding risk, as this is a therapeutic-dose which is higher than that used for post-operative VTE prevention.

Patients Receiving Apixaban

Pre-Operative Management (Table 2):

- **Minor surgery/procedure (LOW BLEEDING RISK):** In patients who require a minor dental procedure, cataract procedure, or minor skin procedure; it is likely safe not to interrupt anticoagulation (as is done in warfarin-treated patients) but data to support such practice is lacking. An alternative approach would be to hold apixaban on the day of the procedure or, if apixaban is not interrupted, to delay that day's dose for 4-6 hours after the procedure.
- **MODERATE BLEEDING RISK procedure**: Stop apixaban 1 day before surgery/procedure (i.e. skip 2 doses), which corresponds to approximately 2-3 half-lives elapsed between stopping apixaban and surgery.
- **Major surgery/procedure including neuraxial anesthesia (HIGH BLEEDING RISK)**: Stop apixaban 2 days before surgery (i.e. skip 4 doses), which corresponds to approximately 4-5 half-lives elapsed between stopping apixaban and surgery.

Post-Operative Management (Table 3):

Resumption of apixaban 5 mg twice daily should be done cautiously after major surgery or in patients at increased bleeding risk, as this is a therapeutic-dose which is higher than that for post-operative VTE prevention.

Patients Receiving Edoxaban

Pre-Operative Management (Table 2):

- **Minor surgery/procedure (LOW BLEEDING RISK):** In patients who require a minor dental procedure, cataract procedure, or minor skin procedure; it is likely safe not to interrupt anticoagulation (as is done in warfarin-treated patients) but data to support such practice is lacking. An alternative approach would be to hold edoxaban on the day of the procedure or, if edoxaban is not interrupted, to delay that day's dose for 4-6 hours after the procedure.
- **MODERATE BLEEDING RISK procedure:** Stop edoxaban 1 day before surgery/procedure (i.e. skip 1 dose), which corresponds to approximately 2-3 half-lives elapsed between stopping edoxaban and surgery.

- **Major surgery/procedure including neuraxial anesthesia (HIGH BLEEDING RISK)**: Stop edoxaban 2 days before surgery (i.e. skip 2 doses), which corresponds to approximately 4-5 half-lives elapsed between stopping edoxaban and surgery.

Post-Operative Management (Table 3):

Resumption of edoxaban 60 mg or 30 mg daily should be done cautiously after major surgery or in patients at increased bleeding risk, as this is a therapeutic-dose.

TABLE 1: BLEEDING RISK FOR VARIOUS INVASIVE/SURGICAL PROCEDURES

LOW/VERY LOW RISK	MODERATE RISK	HIGH RISK
• Dental extractions (1 or 2 teeth), endodontic (root canal) procedure, • Subgingival scaling or other cleaning • Cataract surgery • Dermatologic procedures (e.g. biopsy) • Gastroscopy or colonoscopy without biopsies • Coronary angiography • Permanent pacemaker insertion or internal defibrillator placement (if bridging anticoagulation is not used) • Selected procedures (e.g. thoracentesis, paracentesis, arthrocentesis)	• Other intra-abdominal surgery (e.g. laparoscopic cholecystectomy, hernia repair, colon resection) • Other general surgery (e.g. breast) • Other intrathoracic surgery • Other orthopedic surgery • Other vascular surgery • Non-cataract ophthalmologic surgery • Gastroscopy or colonoscopy with biopsies • Selected procedures (e.g. bone marrow biopsy, lymph node biopsy) • Complex dental procedure (e.g. multiple tooth extractions)	• Any surgery or procedure with neuraxial (spinal or epidural) anesthesia • Neurosurgery (intracranial or spinal) • Cardiac surgery (e.g. CABG, heart valve replacement) • Major intra-abdominal surgery (e.g. intestinal anastomosis) • Major vascular surgery (e.g. aortic aneurysm repair, aortofemoral bypass) • Major orthopedic surgery (e.g. hip or knee replacement) • Lung resection surgery • Urological surgery (e.g. prostatectomy, bladder tumour resection) • Extensive cancer surgery (e.g. pancreas, liver) • Reconstructive plastic surgery • Selected procedures (e.g. kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)

TABLE 2: SUGGESTED PRE-OPERATIVE MANAGEME NT OF PATIENTS TAKING A DOAC

DRUG (DOSE REGIMEN)	RENAL FUNCTION	MODERATE BLEEDING RISK SURGERY/PROCEDURE* *12-25% residual anticoagulant effect at time of surgery acceptable*	MAJOR SURGERY/PROCEDURE INCLUDING NEURAXIAL PROCEDURES*† (HIGH BLEEDING RISK) *<10% residual anticoagulant effect at time of surgery acceptable*
Dabigatran (twice daily)			
	Normal renal function or mild impairment (CrCl ≥50 mL/min) $t_{1/2}$ 7-17 hours	Give last dose 2 days before surgery/procedure (i.e. skip 2 doses)	Give last dose 3 days before surgery/procedure (i.e. skip 4 doses)
	Moderate renal impairment (CrCl 30-49 mL/min) $t_{1/2}$ 17-20 hours	Give last dose 3 days before surgery/ procedure (i.e. skip 4 doses)	Give last dose 5 days before surgery/procedure (i.e. skip 8 doses)
Rivaroxaban (once daily)			
	Normal renal function, mild or moderate impairment (CrCl ≥30 mL/min) $t_{1/2}$ 7-11 hours	Give last dose 2 days before surgery/procedure (i.e. skip 1 dose)	Give last dose 3 days before surgery/procedure (i.e. skip 2 doses)
Apixaban (twice daily)			
	Normal renal function, mild or moderate impairment (CrCl ≥30 mL/min) $t_{1/2}$ 8-12 hours	Give last dose 2 days before surgery/procedure (i.e. skip 2 doses)	Give last dose 3 days before surgery/procedure (i.e. skip 4 doses)
Edoxaban (once daily)			
	Normal renal function, mild or moderate impairment (CrCl ≥30 mL/min) $t_{1/2}$ 10-14 hours	Give last dose 2 days before surgery/procedure (i.e. skip 1 dose)	Give last dose 3 days before surgery/procedure (i.e. skip 2 doses)

*No anticoagulant taken on the day of surgery/procedure. †Neuraxial procedures include spinal anesthesia, epidural catheter insertion and epidural catheter removal.

TABLE 3. SUGGESTED GUIDE FOR *POST-OPERATIVE* MANAGEMENT OF PATIENTS RECEIVING A DOAC

DRUG	MODERATE BLEEDING RISK SURGERY/PROCEDURE (MODERATE BLEEDING RISK)	MAJOR SURGERY/PROCEDURE (HIGH BLEEDING RISK)
Dabigatran	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim
Rivaroxaban	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim
Apixaban	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim
Edoxaban	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim

SPECIAL CONSIDERATIONS:

Patients with Impaired Renal Function:

An approach to managing patients with mild-to-moderate renal dysfunction is shown in **Table 2,** but for patients with severe renal dysfunction who are generally ineligible for DOACs, perioperative management is unclear.

Need for Bridging in DOAC-treated Patients:

In general, the rapid offset and onset of action of DOACs obviates the need for 'heparin bridging' as is done in selected warfarin-treated patients.

Pediatrics:

There are no studies evaluating the use of DOACs in children, although studies are underway. DOACs in children are not recommended until dosing, safety and efficacy are confirmed.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

- Apixaban (Eliquis®)
- Dabigatran (Pradaxa®)
- Edoxaban (Lixiana®)
- NOACs/DOACs: Coagulation Tests
- NOACs/DOACs: Comparison and Frequently Asked Questions
- Rivaroxaban (Xarelto®)

THE CANADIAN DENTAL HYGIENISTS ASSOCIATION
L'ASSOCIATION CANADIENNE DES HYGIÉNISTES DENTAIRES
CDHA ACHD
DENTAL HYGIENE CANADA

Impaired in the Chair?

Cannabis Use and Dental Hygiene Appointments

Cannabis use has many side effects that vary based on the person and potency. These can have implications for both oral health and professional dental hygiene care. In some cases, dental hygiene appointments may need to be rescheduled to minimize risk. Consider the following side effects:

Fast heart rate and anxiety

Cannabis increases the heart rate and heightens anxiety. These side effects may worsen or last longer with anesthetics used for dental hygiene treatment.

Confusion and lack of focus

Cannabis use before a dental hygiene appointment may impair judgement and the capacity to provide consent to treatment.

Interaction with medications

Cannabis may alter the effectiveness of prescribed medications.

Dry mouth and the munchies

Cannabis reduces saliva, leading to dry mouth. It also stimulates food cravings, which increase the amount of time your teeth are exposed to sugars. As a result, cannabis users have a higher risk of cavities, gum disease, and oral infections.

Increased bleeding

Cannabis may increase bleeding and complicate dental hygiene care. Healing may also be affected.

Have a conversation!
Cannabis use is an important part of the health record review.

INTRA-ORAL EFFECTS OF DRUGS

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I. EFFECTS OF DRUGS ON THE SALIVARY GLANDS

A. AUTONOMIC INNERVATION OF SALIVARY GLANDS

BLOOD VESSELS:
Sympathetic alpha = constriction
Parasympathetic response = dilation

SALIVARY GLANDS:
Sympathetic alpha & beta = viscous secretions, amylase secretion
Parasympathetic response = profuse, watery secretions

B. PTYALISM / SIALORRHEA

alprazolam (Xanax®)	clonidine (Catapres)	levodopa (Sinemet)	clozapine (Clozaril)
pilocarpine (Isopto-Carpine)	lithium (Eskalith)	pentoxifylline (Trental)	haloperidol (Haldol)
lorazepam (Ativan)	reserpine (Serpasil)	valproic acid (Depakene)	risperidone (Risperdal)
tacrine (Cognex)	bethanechol (Urecholine)	donepezil (Aricept)	galantamine (Reminyl)

C. XEROSTOMIA

i) <u>Mechanism of xerostomic drug action:</u>

1) Interference with transmission at the parasympathetic neuro-effector junction
2) Interference with transmission at autonomic ganglia
3) Actions at the adrenergic neuro-effector junction
4) Depression of central connections of autonomic nervous system = CNS depressants

ii) <u>Clinical symptoms of xerostomia:</u>

- generalized burning sensation in the mouth
- sore, burning tongue
- generalized oral soreness
- repeated oral abrasions & ulcerations (especially associated with denture wearing)
- difficulty swallowing or speaking due to dry tissues
- swelling of the face
- disturbed sleep patterns

iii) <u>Clinical signs of xerostomia:</u>

generalized mucosal inflammation
- mucosal atrophy
- fissuring of the tongue
- predisposition to ulceration
- infection by *Candida albicans* & angular cheilitis
- retrograde infection of the salivary glands
- increased rate of dental caries (especially root caries)
- increased plaque formation & accumulation

iv) <u>Effects on quality of life:</u>

- increased incidence of oral candidosis
- increased caries and periodontal disease
- decreased nutritional intake
- reduced denture wearing time
- burning mouth, sore tongue, discomfort
- decreased compliance with medications

D. DRUGS WHICH FREQUENTLY CAUSE XEROSTOMIA:

ANTICHOLINERGICS & ANTIPARKINSONIAN AGENTS

methantheline bromide (Banthine)	dicyclomine (Bentyl)	trihexyphenidyl (Artane)
benztropine mesylate (Cogentin)	tolterodine (Detrol)	**oxybutynin (Ditropan)**

ANTIDEPRESSANTS

amitriptyline (Elavil)	SSRI's & others	buproprion (Wellbutrin)
trazodone (Desyrel)	MAOI's	**ALL TCAs**

SYSTEMIC ANTIHISTAMINES

diphenhydramine (Benadryl)	clemastine (Tavist)	hydroxyzine (Atarax)
chlorpheniramine (Chlor-Trimeton)	triprolidine (Actifed)	cetirizine (Zyrtec-OTC)

ANTIPSYCHOTICS

chlorpromazine (Thorazine)	**thioridazine (Mellaril)**	prochlorperazine (Compazine)
haloperidol (Haldol)	thiothixene (Navane)	trifluoperazine (Stelazine)

ANTIHYPERTENSIVES

ACE INHIBITORS	BETA BLOCKERS	ALPHA BLOCKERS
ARBs	**guanethidine (Ismelin)**	**reserpine (Serpasil)**

CNS STIMULANTS	amphetamines	**phentermine (Fastin)**
diethylproprion (Tenuate)	methylphenidate (Ritalin, Concerta)	pseudoephedrine (Sudafed)

DIURETICS

chlorthalidone (Hygroton)	ALL THIAZIDES	**ALL LOOP DIURETICS**
K+ SPARING AGENTS	**furosemide (Lasix)**	**bumetanide (Bumex)**

MISCELLANEOUS AGENTS	systemic bronchodilators	OPIOID ANALGESICS
muscle relaxants	**anticholinergic**s	hypotensive agents

E. OTHER CONDITIONS ASSOCIATED WITH XEROSTOMIA

NONPHARMACOLOGIC CAUSES OF DRY MOUTH

Cause	Facts to Note
Accidental or surgical trauma	Results from damage to nerves that supply sensation to mouth; intact salivary glands need innervation to function normally.
Autoimmune or chronic disease	Sjögren's syndrome causes xerostomia concomitantly with xerophthalmia. Sarcoidosis, Eaton-Lambert syndrome (myasthenic syndrome), systemic lupus erythematosus, amyloidosis, and HIV (especially in children) may also cause xerostomia.
Bone marrow transplant	Occurs in up to 60% of bone marrow transplant recipients.
Endocrine disorders	Frequently results from poorly controlled diabetes.
Hyposecretory conditions	Primary biliary cirrhosis, atrophic gastritis, and pancreatic insufficiency.
Mental illness	Often associated with stress, anxiety, and/or depression.
Radiation	Radiation at or near (eg, within inches of) salivary glands can damage them temporarily or permanently. Radiation doses of 25 to 30 Gy cause severe, permanent dryness (cancer cells require a cumulative dose of 40 to 70 Gy to be killed). Lower doses usually disrupt salivary flow temporarily by 60% to 70% within 1 week of treatment. Effective treatment has yet to be identified.

II. MANAGEMENT OF THE XEROSTOMIC PATIENT

A. PATIENT COUNSELING – see two page patient xerostomia handout

Many patients may be successfully managed via lifestyle/habit changes alone

- the last two pages contain a patient information handout that can be duplicated for patients
- all xerostomic patients will benefit from those simple and inexpensive suggestions:

B. SELECTED XEROSTOMIA RELIEF PRODUCTS (* denotes ADA acceptance)

– most are OTC products and individual patient acceptance varies widely

PRODUCT (MFR)	INGREDIENTS	DISPENSED/SOLD	PT. COST
Aquoral Protective Oral Spray (KPharma)	OGT (oxygenated glycerol triester, silicon dioxide,etc.)	Two 10ml aluminum spray vials	$66/2 vials
All Day Dry Mouth Spray (Elevate)	Xylitol, Glycerin, Sodium Polyacrylate, Polyacrylic acid	2 oz spray bottle	$9.45
Basic Bites Neutralizing Chews (Ortek)	Maltitol,Calcium carbonate,diglycerides,palm oil,xylitol	60 or 120 pieces per bag	$19.95/$38.95
GC America Dry Mouth Gel (GC America (800) 323-7063	Polyglycerol 60%, Water 36%, NaCMC 2.5%, five flavors-lemon,mint,orange,raspberry,fruit salad	Dental Office Dispensed Only 40g tubes, order in boxes of 10 tubes	$1.50/tube dentist.net
Lubricity Dry Mouth Spray (Lubricity)	Water, Xylitol, Sodium Hyaluronate, no sweeteners	2 oz spray bottle	$19.95
Mouthkote (Parnell)	xylitol, sorbitol***, yerba santa, citric acid, ascorbic acid, sodium benzoate, saccharin	8 oz pump spray	$9.50
Oasis Mouthwash and Mouth Spray (GlaxoSmithKline-Consumer Healthcare)	Water, glycerin, sorbitol***, poloxamer 338, castor oil, cellulose gum cetylpyridinium chloride (CPC)	16oz bottle mouthwash 1oz spray bottle	$5.99 $4.99
Oral Balance Moisturizing Gel or Liquid (Laclede)	glucose oxidase enzyme system, xylitol, hydroxyethyl cellulose, aloe vera, K thiocynate	42g (1.5 oz) tube of gel 45ml (1.5oz) squeeze bottle	$8.45 $8.45
Salivea Spray(Laclede)	Hydrogenated starch,prop glycol,suflower oil,xylitol	2 oz spray bottle	$7.99
Stoppers4 Dry Mouth Spray (Woodridge)	Water, glycerin, xylitol,hydroxyethylcellulose,lysozyme, lactoferrin,glucose oxidase	1oz spray bottle	$6.09

Oralbalance® (Laclede) – Moisturizing gel in 1.5 oz tube, Moisturizing liquid in 1.5oz squeeze bottle

- moisturizing gel, especially useful at nighttime, liquid is for daytime use
- spread on tissues and under dentures as needed for long-lasting effects
- high patient acceptance, slightly sweet flavor, beneficial ingredients

C. SALIVA STIMULANTS

1. OVER THE COUNTER

- Dentiva, OraMoist, Sal-Ese, Smart Mouth Mints and Xylimelts discs may give symptom relief
- **SalivaSure®** Tablets (fomerly called Salix SST® by-Scandinavian Formulas, Inc.)-90 ct. bottle $8.95
  - xylitol, citric acid, apple acid, Nacitrate, NaCMC, Dibasic calcium phosphate, colloidal silica
  - buffered citric acid tablets for salivary stimulation without hard tissue demineralization
  - order at www.scandinavianformulas.com- easy to carry, pleasant flavor, well-accepted by patients
  - ***our most highly recommended product, no drug interactions or adverse effects***

2. SYSTEMIC CHOLINERGIC AGENTS

For all cholinergic products:

- titrate to minimum effective dose
- potent cholinergic agonist -must counsel patients as to side effects and signs of toxicity
- contraindicated in patients with narrow-angle glaucoma or cardiovascular disease as well patients on beta-blockers (may cause conduction disturbance) or anticholinergics
- use with caution in patients with gall stones, biliary tract disease, nephrolithiasis or pulmonary disease
- prescribe in consultation with patient's physician

RX: **Pilocarpine 4% ophthalmic solution**
Sig: Place 2-4 drops in 1-2 tablespoons of water, swish and swallow up to QID

- 4% solution = 1.3mg/drop, available in 15 ml bottles
- dose can be placed on sugarless gum
- advantages: can titrate to effect, inexpensive ($12)

RX: **Pilocarpine 5mg & 7.5 mg tabs (Salagen®)**
Sig: 1 tab PO TID

- disadvantages: unscored tablet
- can't titrate to effect =the biggest disadvantage
- Tier 2 expensive (5mg $50/90 tabs, 7.5mg $80/90 tabs)

AVAILABLE GENERICALLY!

RX: **Cevimeline (Evoxac® , g) 30mg capsules**
Sig: Take one capsule BID-TID
AVAILABLE GENERICALLY

- more selective for salivary gland receptors
- may be safer from cardiac standpoint
- giving with food extends action
- $80/90 caps GoodRx

D. CARIES PREVENTION:

- ***OTC FLUORIDES:***
  - 0.02% rinse (from 0.05% NaF) - Act® Anti-cavity, Fluorigard®
  - 0.l% gels (from 0.4% SnF) - generics OTC, Gel-Kam® & Stop® are Rx, etc
    - increased staining from SnF in xerostomic patients and acidic pH can be irritating
    - fluoride concentration is equivalent to most OTC dentifrices
    - ***we do not use stannous fluoride preps for xerostomic patients***

- ***PRESCRIPTION FLUORIDES (higher concentration):***
  - 0.09% rinse (from 0.2% NaF) - Fluorinse®, Prevident, Neutracare, etc.
  - 0.5% neutral gel (from 1.1% NaF) - Prevident®, Neutracare, etc. - brush on or tray delivery
  - Prevident 5000 Dry Mouth® - combination mild dentifrice (RDA 87) & high potency fluoride treatment (1.1% NaF) in a single product – highly recommended for BID use in the xerostomics

- **Xylitol –January 2013 JADA study on adult use of 1gram 5x daily was surprising!**
  - **Previous studies on children showed benefit but definitive effect was inconclusive**

E. SALIVA ENHANCEMENT OR MINERALIZING PRODUCT

1) Novamin (calcium sodium phosphosilicate) by NovaMin

A synthetic mineral composed of calcium, sodium, phosphorous and silica, all elements naturally occurring in the body. Silica (glass) containing Ca and PO is the driving mechanism that binds to the tooth surface

2) Recaldent (casein phosphopeptide-amorphous calcium phosphate)

Casein phosphopeptide and amorphous calcium phosphate (CPP-ACP)
Casein phosphopeptide is a milk protein peptide that is bound to amorphous calcium phosphate

3) Tri-Calcium Phosphate & NaF 5000ppm is ClinPro

4) Arginine Bicarbonate and Calcium Carbonate (Sensistat is now Colgate Pro-Argin)

Arginine bicarbonate is an amino acid complex found in saliva that is bound to calcium carbonate
Pro-Relief with Pro-Argin by Colgate
Proclude (Ortek) & Denclude (Ortek)

5) Supersaturated Calcium Phosphate Oral Rinses

-CAPHOSOL – solution in ampules and is a medical "device"

Caphosol® is indicated as an adjunct to standard oral care in treating oral mucositis caused by radiation or high dose chemotherapy. Relief of dryness of the oral mucosa in these conditions is associated with an amelioration of pain. Caphosol® is also indicated for xerostomia.Very expensive and dispersible tablets available in UK and Australia.

-SALIVAMAX – powder packets to be dissolved in 30ml of water prior to use

SalivaMAX™ may be used for the relief of dryness of the oral mucosa when hyposalivation results from the following: pre/post surgery, radiotherapy, chemotherapy, infection or dysfunction of the salivary glands.

-NEUTRASAL-powder packets to be dissolved in 30ml of water prior to use

NeutraSal is indicated for dryness of the mouth (hyposalivation, xerostomia); NeutraSal is also indicated for dryness of the oral mucosa due to drugs such as antihistamines or atropine or other anticholinergic agents that suppress salivary secretion; NeutraSal may be used as part of an oral hygiene program for patients with dry mouth.

III. AGENTS CAUSING INCREASED GAG REFLEX

- ✓ Statins" used to manage hypercholesterolemia (Mevacor, Zocor, Lipitor, etc)
- ✓ Potassium-sparing diuretics (triamterene, spironolactone, amiloride)
- ✓ Cholestyramine (Questran, g) – resin for hypercholesterolemia
- ✓ Buproprion (Wellbutrin, g) – antidepressant, anti-smoking

IV. DRUGS WITH DIRECT EFFECTS IN THE ORAL CAVITY

TOOTH DISCOLORATION (EXTRINSIC) stannous fluoride chlorhexidine iron preparations
(INTRINSIC) fluoride tetracyclines

BLACK HAIRY TONGUE

amitriptyline (Elavil)	diazepam (Valium)	nitrofurantoin (Macrodantin)	tetracycline (Sumycin)
Amoxicillin (Amoxil)	hydrogen peroxide	nortriptyline (Aventyl)	
cyclobenzaprine (Flexeril)	ketoprofen (Orudis)	PHENOTHIAZINES	
clonazepam (Klonopin)	lorazepam (Ativan)	penicillin VK	

GINGIVAL OVERGROWTH

amiodarone (Cordarone, Pacerone) ORAL CONTRACEPTIVES **PHENYTOIN (DILANTIN,G)**
cyclosporine (Sandimmune, Neoral) **CALCIUMCHANNELBLOCKERS VALPROICACID(Depakene,Depakote**

PIGMENTATION

busulphan (Myleran)	HEAVY METALS (Hg, Pb)	phenytoin (Dilantin)
bismuth (Pepto-Bismol)	methotrexate (Rheumatrex)	PROGESTINS
cyclophosphamide (Cytoxan)	PHENOTHIAZINES	rifabutin/rifampin
clofazimine (Lamprene)	hydroxychloroquine	tetracyclines (Minocin, g)

SOFT TISSUE ULCERATION

ACE INHIBITORS	carbamazepine	ipratropium (Atrovent)	potassium chloride
abacavir (Ziagen)	cocaine	iron salts	warfarin (Coumadin)
actinomycin D (Cosmegen)	Echinacea	leflunomide (Arava)	zalcitabine (Hivid)
alendronate (Fosamax)	feverfew	methotrexate (Folex, Rheumatrex)	zidovudine (Retrovir)
ampicillin (Omnipen)	flavoring oils	modafinil (Provigil)	
aspirin	fluorouracil (Adrucil)	NSAIDs	
bleomycin (Blenoxane)	genitian violet	pancrelipase (Creon)	

CONSEQUENCES OF IMMUNOSUPPRESSION – bacterial, viral and fungal proliferation

Antibiotics: extended and broad spectrum antibiotics including cephalosporins and amoxicillin/clavulanate

Biologics: Anakinra(Kineret),Leflunomide(Arava), Methotrexate,Rituximab(Rituxan),Tacrolimus,Tocilizumab

Corticosteroids: systemic prednisone or methylprednisolone. Inhaled flunisolide, betamethasone, or triamcinolone

TNFIs: Adalimumab(Humira),Certilizumab(Cimzia),Etanercept(Enbrel),Golimumab(Simponi),Inflixumab(Remicade)

V. DRUGS AFFECTING TASTE AND SMELL

D= Dysgeusia-Altered taste M=Metallic Dysgeusia B=Bitter Dysgeusia
A=Ageusia-Absence or impairment of taste H=Hypogeusia-decreases sensitivity to taste S=Sweet Dysgeusia
5-flourouracil (Adrucil) D,S

Acebutolol (Sectral) D
acetazolamide (Diamox) D,B
allopurinol (Zyloprim)
amiloride (Midaamor)-to salt H
amiodarone (Cordarone) D
AMPHETAMINES
amphotericin B (Fungizone) D,H
amrinone (Inocor) D,H
atenolol (Tenormin) D
auranofin (Ridaura) D,M
aurothioglucose (Solganal) D
azathioprine (Imuran) D
azelastine (Astelin) D,B
baclofen (Lioresal) D
BENZODIAZEPINES B, M
benzphetamine (Didrex) D
BETA LACTAM ANTIBIOTICS M
betaxolol (Kerlone) D
bisoprolol (Zebeta) D
bleomycin (Blenoxane) D,A
bretylium (Bretylol) D,H
brinzolamide (Azopt) B
bromocriptine (Parlodel) M
calcifediol (Calderol) M
captopril (Capoten) D,M
carbamazepine (Tegretol) D,H
carboplatin (Paraplatin) M,H
cartcolol (Cartrol) D
cefamandol (Mandol) D
chlorhexidine (Peridex) D,M,B,H
chloestyramine (Questran) D
chloline magnesuim trisalicylate (Trilisate,Tricosal)A
cisplatin (Platinol) M,A,H
clarithromycin (Biaxin) D
cloffibrate (Atromid-S) D
cromolyn sodium (Intal, Nasalcrom) D
dextroamphetamine (Dexedrine) D
diazoxide (Proglycem) D
dicyclomine (Bentyl, Di-Spaz) A
diethylopropion (Tenuate) D
diltiazem (Cardizem) D,B,H
dipyridamole (Persantine) D
dolasetron (Anzemet)
EDTA (Chealamide, Disotate, Endrate) D
enalapril (Vasotec) D,A
encinide (Enkaid)D
ethambutol (Myambutol) M
ethionamide (Trecator-SC) M
etidronate (Didronel) M,A
flecainide (Tambocor) D
flunisolide (AeroBid, Nasalide) A
flurazepam (Dalmane) M
fomepizole (Antizol) M
glycopyrrolate (Robinol) A
granisetron (Kytril) D
griseofulvin (Fulvicin) D
hydrochlorothiazide (Esidrix, Microzide, Oretic) A
hyoscyamine (Anaspaz) A
interferon-gamma A
iodine M
iron (various vitamins) D
iron dextran (Dexferrum) M
isotretinoin (Accutane) A
levamisole (Ergamisol) M
levobupivacaine M
levoldopa (Dopar) D,H
lincomycin (Lincocin) D
lisinopril (Prinvil, Zestril) D
lithium (Eskalith, Lithane) D,M
lomefloxacin A
lovastatin (Mevacor) A
mazindol (Sanorex, Mazanor) D
mechlorethamine (Mustargen) M
metformin (Glucophage) D,M
methimazole (Tapazole) D,A
methocarbamol (Delaxin) M
methotrexate (Folex) D
metronidazole (Flagyl) D,M,H
mexiletine (Mexitil) D
midazolam (Versed) D
moricizine (Ethmozine) D
nadolol (Corgard) D
nicotine polacrilex (Nicorette) D
nifedipine (Procardia) D,A,H
nitroglycerin (Nitrostat) D
ofloxacin (Floxin) A
ondansetron (Zofran) D
OPIATES A
penbutolol (Levatol) D
penicillamine (Cuprimine) D,M
pentamidine (NebuPent) M
phendimetrazine (Anorex, Bontril) D
pergolide (Permax) D
phentermine (Ionamin) D
phenylbutazone (Butazoldin) D,A
pindolol (Visken) D
plicamycin (Mithracin) M
potassium iodide (Pima, Thyro-Block) M
procaine penicillin (Wycillin) D,M
procainimide (Pronestyl) D
propafenone (Rythomol) D,M
propranolol (Inderal) D,A
propylthiouracil (PTU) D,B,H
rifabutin (Mycobutin) A
selegiline (Elderpryl) D
selenium (Selepen) M
spironolactone (Aldactone) D,B
sulfasalazine (PTU) H
terbinafine (Daskil,Lamisil) A
tetracycline (Achomycin) D,M
timolol (Blocadren) D
tocainide (Tonocard) M
tolbutamide (Orinase) D
troazolam (Halcion) A
vincristine (Oncovin) D
venlafaxine (Effexor) 2% D

VI. DRUGS CAUSING HALITOSIS

AMPHETAMINES
ANTIHISTAMINES
ANTINEOPLASTICS
amyl nitrite
chloral hydrate (Noctec)
disulfuram (Antabuse)
DIURETICS
DMSO
ethyl alcohol
garlic (non-dessicated)
griseolfulvin (Fulvicin)
isosorbide dinitrate (Isordil)
lithium (Eskalith, Lithane)
penicillamine (Cuprimine)
PHENOTHIAZINES
selenium
TRANQUILIZERS
xerogenic drugs

VII. IDIOSYNCRATIC DRUG ERUPTIONS

LICHENOID ERUPTIONS

ACE INHIBITORS
acyclovir (Zovirax)
allopurinol (Zyloprim,g)
BETA BLOCKERS
carbamazepine
chloroquine (Aralen)
chlorprompamide (Diabinese)
furosemide (Lasix,g)
gold salts
HMG CoA "Statins"
NSAIDS
PHENOTHIAZINES
SULFONYLUREAS
TETRACYCLINES
THIAZIDE DIURETICS
quinidine (Duraquin, Cardioquin)
quinine (Formula Q)
tolbutamide (Orinase)
tripolidine (Actagen-C)

FIXED DRUG ERUPTIONS

BARBITURATES (Amytal, Seconal)
chlordiazepoxide (Librium)
SULFONAMIDES (Gantrisin, Gantanol, Bactrim, Septra)
TETRACYCLINES (Doxycycline, Minocycline, Tetracycline)

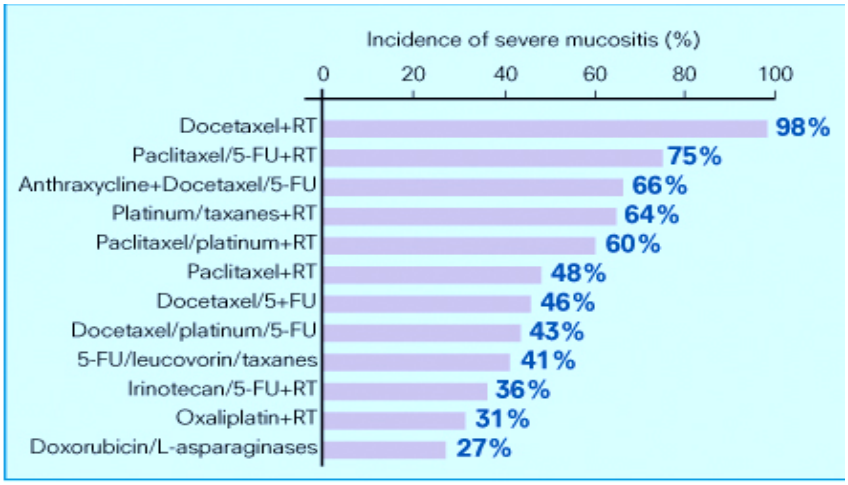
ERYTHEMA MULTIFORME

aspirin
acyclovir (Zovirax)
ampho B (Amphocin)
BARBITURATES
bupropion (Wellbutrin, Zyban)
carbamazepine (Tegretol)
clomiphene (Cloimid)
danazol (Danocrine)
diltiazem (Cardizem)
Echinacea
efavirenz (Sustiva)
enalapril (Vasotec)
meropenem (Meronem)
methazolamide (GlaucTabs)
methotrexate (Folex, Rheumatrex)
methylphenidate (Ritalin)
midodrine (ProAmatine)
nifedipine (Procardia)
ranitidine (Tritec)
sulfacytine (Renoquid)
sulfadiazine (Microsulfon)
SULFONAMIDES
tamoxifin (Nolvadex)
tetanus toxoid

DISSEMINATED LUPUS ERYTHEMATOSUS

hydralazine (Apresoline)
isoniazid(INH)
methyldopa (Aldomet)
phenytoin (Dilantin)

CANCER CHEMOTHERAPY-INDUCED MUCOSITIS



Antineoplastic therapies with an incidence of severe (Grade 3 and 4) mucositis.

VIII. DRUG-INDUCED MOVEMENT DISORDERS

Add/Adhd Drugs – atomoxetine (Straterra), Methylphenidate (Concerta, Metadate, Ritalin)
Antidepressants – SSRIs (Prozac, Paxil, Zoloft, Celexa, Lexapro), TCAs (amitriptyline,nortriptyline), Lithium
Metoclopramide (Reglan), First and Second Generation Antipsychotics – tardive dyskinesia

IX. OSTEONECROSIS OF THE JAW (ONJ) FROM BISPHOSPHONATES

Bisphosphonates – IV: pamidronate (Aredia), zoledronate (Zometa)-used for bone mets/hypercalcemia
ORAL:alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)
IV: zoledronate (Reclast) – once a year 5mg infusion for treatment of osteoporosis
Rank Ligand Inhibitor: for osteoporosis or cancer patients with bone mets,
SQ: denosumab (Prolia) is a 60mg every 6 mo RANKL inhibitor. Effects on bone are reversible on d/c.
SQ: denosumab (Xgeva) is a 120mg every 4 weeks RANKL inhibitor used for certain cancer patients

MOA-Bisphosphonates inhibit osteoclast precursors from attaching to the mineralized matrix which blocks transformation into mature osteoclasts (bone-eroding cells). This allows osteoblasts (bone-building cells) to work. Rank ligand inhibitors also inhibit osteoclasts so both classes can cause MRONJ.

Osteoanabolic Agents-teraparatide (Forteo) & abaloparatide (Tymlos) – can IMPROVE MRONJ!
Use is limited to 24 months due to possible risk of osteosarcoma

Sclerostin Blocker – romosozumab (Evenity) – newest agent and primarily to treat spinal fractures
Use is limited to 12 months as the anabolic effect on bone wanes after 12 mo.

Antiangiogenic Agents or Growth Factor Inhibitors that impair wound healing

Pharmaceutical agents associated with MRONJ	Mode of action
For Oncologic use	(all these compounds affect angiogenesis)
Imatinib, Sunitinib (Sutent)	Tyrosine kinase inhibitors
Sorafenib (Nexavar)	VEGF inhibitor
Bevacizumab (Avastin)	Angiogenic inhibitor

ONJ Etiology – Osteoclast formation is the first step in bone healing so this process is inhibited by bisphosphonates. Rank ligand inhibitors also inhibit osteoclast formation. Antiangiogenesis and growth factor inhibitors affect bone healing in high bone turnover rate areas such as the mandible.

ONJ Signs and Sx-undiagnosed pain, jaw numbness or heaviness, mucosa fails to heal, soft tissue swelling or infection

ONJ Risk Factors-dental extraction, dental infection or other trauma, drug therapy with corticosteroids, cancer chemotherapy, intravenous bisphosphonates such as Zometa or Aredia, oral bisphosphonates (Fosamax, Actonel, Boniva)

ONJ Characteristics-exposed bone is very painful, swelling and loosening of teeth may be seen, debridement and surgical correction exacerbate lesions, many cases are complicated by infection, primary risk is cancer patients on IV bisphosphonates

ONJ Prevention-avoid elective osseous surgery, recommend panoramic radiograph prior to tx., remove abscessed and diseased tissue, dental prophylaxis and stabilization appropriate, ensure proper denture fit, oral hygiene self-care education

Treatment Modifications for Bisphosphonate patients-check and adjust dentures, aggressively manage dental infections nonsurgically with endodontic tx or minimal surgery, endodontic therapy is far preferable to extractions when possible

ONJ Therapy-antibiotics, alcohol free chlorhexidine, conservative debridement of sequestering bone

Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment

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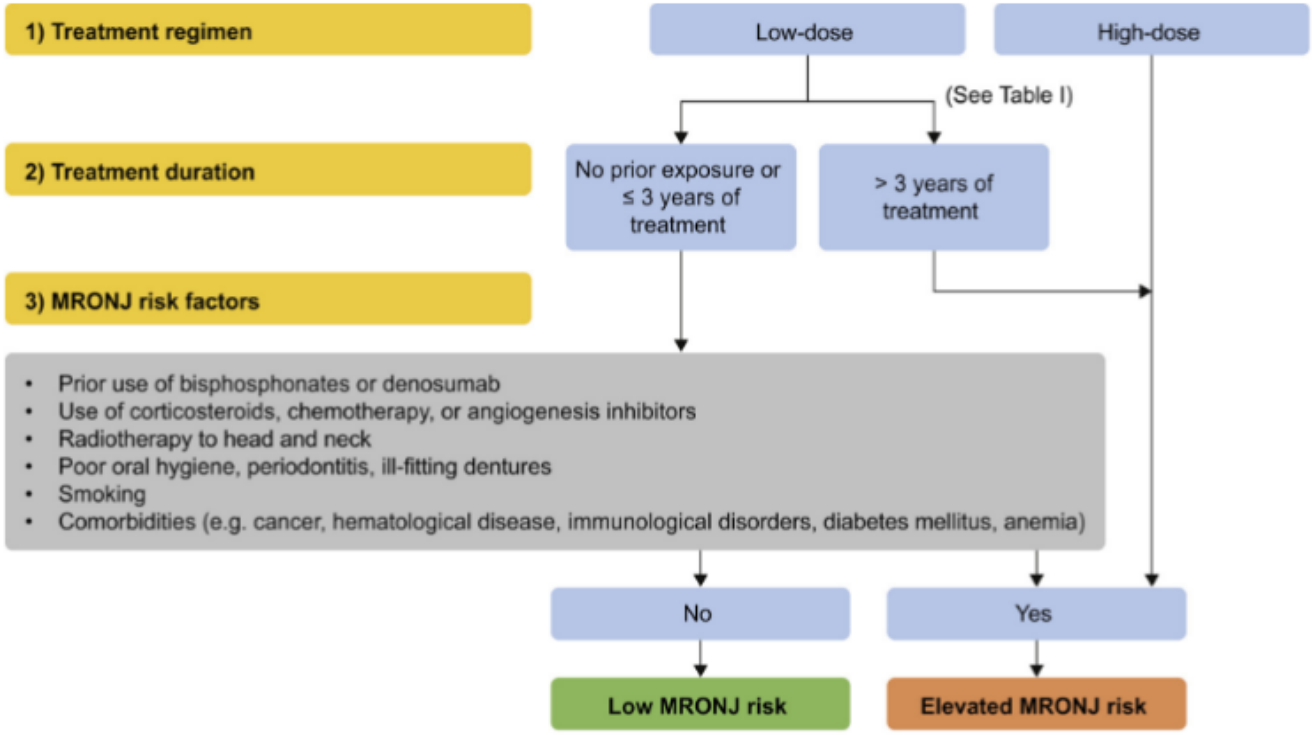
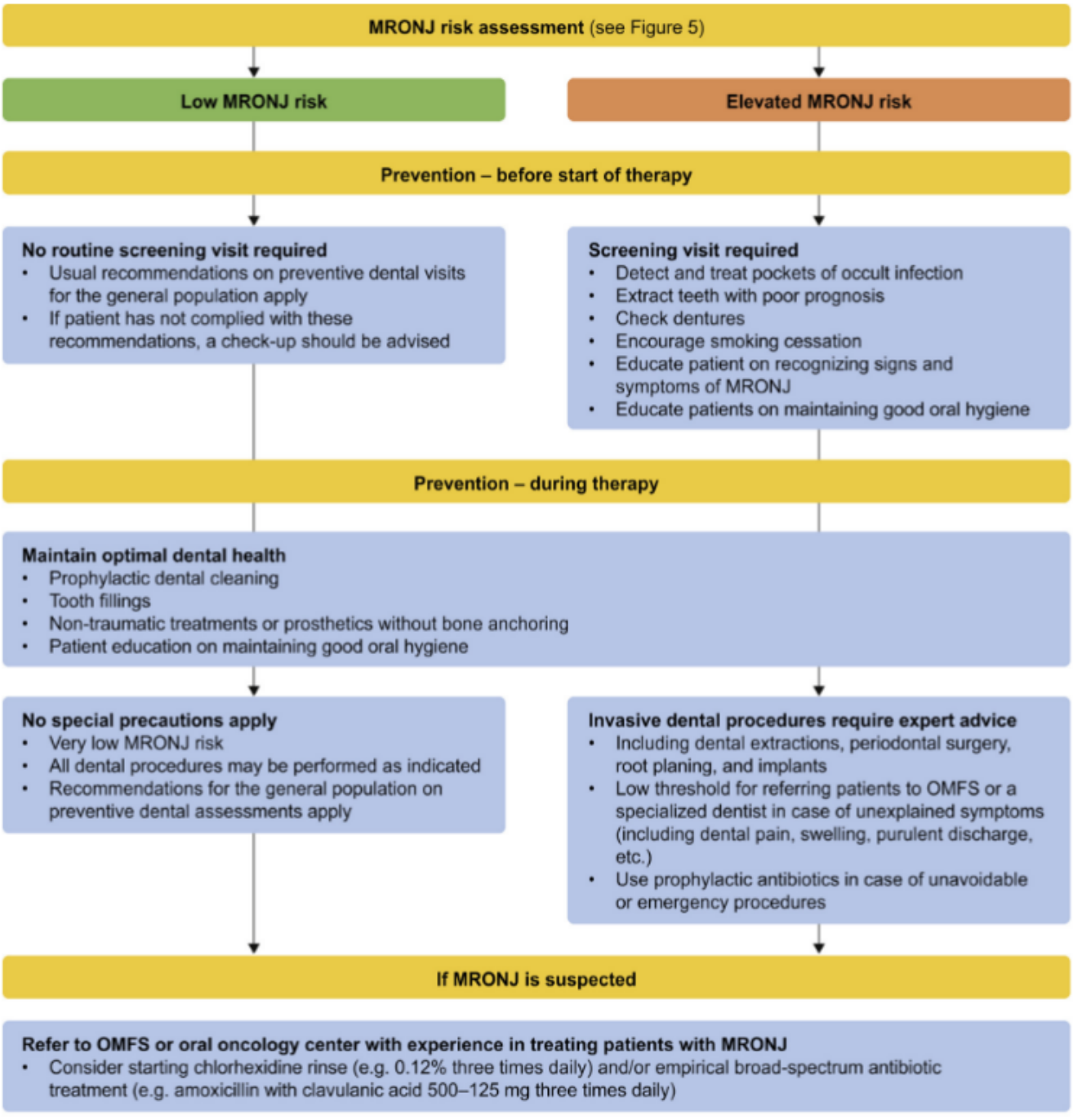
Skeletal complications caused by osteoporosis or bone metastases are associated with considerable pain, increased mortality, and reduced quality of life. Furthermore, such events place a burden on health care resources. Agents that prevent bone resorption, such as bisphosphonates or denosumab, can reduce the risk of skeletal-related events and are widely used in patients with osteoporosis or bone metastases of cancer. Medication-related osteonecrosis of the jaw (MRONJ) is a rare, but potentially serious, adverse event associated with high cumulative doses of bisphosphonates or denosumab. However, MRONJ can be treated, and the likelihood of the development of this condition can be reduced through prophylactic dental care and the maintenance of good oral hygiene. Dentists, as part of a multiprofessional team, have a critical role in preventing MRONJ. This review describes the incidence and pathophysiology of MRONJ and provides guidance for dental practitioners with regard to the screening, prophylactic treatment, diagnosis, and management of patients with this condition. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;127:117–135)





IV, intravenous; MRONJ, medication-related osteonecrosis of the jaw; OMFS, oral and maxillofacial surgeon; SC, subcutaneous

Xerostomia (Dry Mouth) Patient Handout

Department of Oral Pathology, Radiology and Medicine
The University of Iowa Colleges of Dentistry and Pharmacy
2025

DEFINITION & CAUSES

Xerostomia (pronounced "zero-sto'me-ah") is the medical word for the sensation of dry mouth often due to decreased or absent saliva. Saliva is important for hydration, lubrication and cleansing in the oral cavity. The components of saliva aid in digestion, maintain the health of the oral mucosa and help prevent tooth decay.

Dry mouth is a common problem and is caused by a variety of medical conditions and medications. Many drugs, including antihistamines, antidepressants, blood pressure medications and opioid analgesics are known to cause xerostomia. Dry mouth can also be caused by head and neck radiation, depression, anxiety and some autoimmune diseases.

HELPFUL SUGGESTIONS

The lifestyle modifications listed below can help relieve dry mouth symptoms.

Avoid the following:

a. Caffeine
   - Daily high doses of caffeine can contribute to dry mouth. Make sure all of your beverages (coffee, tea, etc.) are caffeine free. Alternatively, limit caffeine consumption to 200-400mg per day to limit adverse effects.

b. Alcohol and alcohol containing mouthwashes (read labels carefully)
   - Many commercial mouthwashes contain alcohol which may stimulate salivation but can irritate the tissue.
   - Biotène® and Oasis® make mouth rinses specifically for dry mouth. ACT® Total Care Dry Mouth rinse contains fluoride. Halitosis mouthrinses include CloSysII Silver, SmartMouth DryMouth, and TheraBreath DryMouth

c. Acidic beverages and foods
   - Carbonated beverages, vitamin waters, energy and sports drinks are very acidic. Without the neutralizing ability of saliva, these drinks erode the teeth and can make your mouth sore. Constant sipping of acidic beverages is especially problematic.
   - Foods and candies high in acid content (citrus fruits, tomatoes, lemon drops, etc.) cause dental decay and may irritate the soft tissue of your mouth.

d. Gum, candy, cough drops and beverages that contain sugar
   - Sugar, especially in retentive (sticky) form is very damaging to the teeth. Sucrose feeds bacteria that cause cavities.
   - Look for products that contain xylitol (a sweetener that does not cause cavities). Xylitol gums (Spry®, Xyloburst®) when chewed frequently, may inhibit cavity causing bacteria. Cariostatic dose is 6-10grams/day in 3-5 sessions.
   - Avoid gums, candies and oral care products that contain cinnamon as it is a common irritant.

e. Toothpastes with harsh chemicals or strong flavoring agents
   - Many toothpastes advertised for tartar control, whitening etc. contain pyrophosphates and other chemicals that can damage dry oral tissues. Detergents such as SLS and CMPB (cocamidopropyl betaine) can be irritating.
   - Sodium lauryl sulfate (SLS) is a foaming agent/detergent that is found in many toothpastes. This detergent is well-recognized as a cause of intraoral tenderness and ulceration. We recommend toothpastes that are SLS-free and contain either low levels or no pyrophosphates (Squiggle Enamel Saver Toothpaste, ClosysII with Fluoride, Rembrandt Gentle White Toothpaste, Prevident 5000 Dry Mouth, All Day 5000 Dry Mouth Toothpaste)

Try the following:

a. Hydration - inadequate hydration can be an important factor in having dry mouth symptoms
   - Sip cool water throughout the day, let ice chips melt in your mouth (never chew ice!).
   - Many people don't drink enough fluids and this will contribute to a dry mouth.
   - Constant, <u>daily</u> hydration is very important

b. Try drinking whole or 2% milk with meals.
   - Milk containing fat has moisturizing properties that can aid in swallowing.
   - Patients who cannot drink cow's milk may find similar benefit in almond or soy milk

c. Use a cool air humidifier in the bedroom – clean and change water daily

- Start the humidifier 1-2 hours before bedtime and run continuously throughout the night. The extra humidity can help keep your mouth more comfortable and allow you to sleep through the night. This is of benefit even if you have a humidifier attached to your furnace.

d. For dry lips, highly purified lanolin products (Lansinoh®) are good lip moisturizers.
   - Chronic use of petrolatum type products on dry lips can be counterproductive.
   - Moisturizing lip balms we recommend include Blistex Herbal Answer®, Blistex Complete Moisture or Banana Boat with Aloe Vera and Vitamin E®.
   - Many dry lip products contain chemicals that can cause irritation or dryness. The need to frequently reapply lip balm is a good indicator that the product is not helpful.
e. If possible, sleep on your side to reduce mouth breathing.
f. See your dental practitioner frequently.
   - People with dry mouth are much more prone to oral health problems including oral yeast infections and tooth decay. Excellent oral hygiene is necessary to prevent cavities and gum disease.
   - Your dentist may use tooth sealants, prescription fluoride toothpastes and other interventions that will help prevent oral health problems.
   - Report any unusual oral soreness or burning sensations to your dentist.

COMMERCIAL SALIVA SUBSTITUES, STIMULANTS AND MOISTURIZING GELS & SPRAYS

The products listed below are available without a prescription and can be found or ordered from many pharmacies. These products are often helpful in alleviating the discomfort of dry mouth. They can be used as often as needed and do not interfere or react with other medications. Here are a few examples of products we recommend:

a. SalivaSure™ Tablets (Scandanavian Formulas, Inc) – 90 ct. bottle
   - To stimulate natural saliva flow, dissolve one tablet slowly under tongue up to every hour as needed.
   - Highly recommended, will not cause cavities or sore mouth. Easy to carry, no drug interactions.
   - This product is available at the Dental Pharmacy and does not require a prescription.
b. Biotène® Products (GlaxoSmithKline)
   - Oralbalance® Gel – 1.5 oz tube – has a soothing effect on oral tissue, can be used under dentures to improve comfort. Rinse mouth with water, then spread thin film over affected tissues. Can be used as often as needed.
   - Biotène® Moisturizing Mouth Spray – 1.5 oz. spray bottle. Shake well and spray directly into mouth as needed.
   - Oralbalance® Dry Mouth Moisturizing Liquid – 1.5 oz squeeze bottle. Squeeze several drops directly into mouth as needed.
c. Elevate Oral Care Products – All Day Dry Mouth Spray, All Day Dry Mouth Gel, Epic Toothpaste with Sodium Fluoride
d. Xylimelts-oral adherent discs that stick to your teeth or gums with xylitol that stimulates saliva flow day or night
e. Lubricity Oral Lubricant – contains hyaluronic acid and is a stream, not a spray. No flavors or colors.

COMMERCIAL OVER THE COUNTER (OTC) TOOTHPASTES

Avoid toothpastes that make claims on whitening or tartar control as they often contain ingredients that are irritating to the oral mucosa. Most OTC toothpastes contain detergents (sodium lauryl sulfate (SLS), cocamidopropyl betaine etc.) that irritate oral mucosa as mentioned above. We recommend detergent-free toothpastes:
- Squigle Enamel Saver Toothpaste –contains xylitol and fluoride
- Tom's of Maine for Kids Strawberry with fluoride
- Prevident Dry Mouth 5000ppm toothpaste (RX only)

PROFESSIONALLY DISPENSED PRODUCTS

a. GC Dry Mouth Gel (GC America) – 40 g. tube. Rinse mouth with water, then spread thin film on affected tissue as needed. Similar to Oralbalance® gel. Available in 5 mild flavors.
b. MI Paste™ and MI Paste Plus™ - 40 g. tube. Rinse mouth with water, then spread pea-sized amount over teeth and tissue. (This product requires a prescription from your dentist or physician)
   - These products were developed to help rebuild tooth structure, but have the additional effect of soothing dry intraoral tissue. *Cannot be used by people with casein (milk protein) allergies.*
   - Especially useful at bedtime and probably the best product for "comfort" that we have right now.
C. Neutragel 1.1% NaF Gel by Germiphene is unflavored & unsweetened; X-Pur 1.1%NaF gel by Oral Science is mild mint

PRODUCTS FOR MANAGING ORAL MALODOR

I. CAUSES OF ORAL MALODOR

A. Non-oral causes
-Systemic Sources – diabetes, high protein/low carb diets, renal or hepatic failure, sinus infections, internal bleeding
-Medications that cause malodor – Antabuse, DMSO, Griseofulvin, Isosorbide dinitrate
-Xerogenic Medications – antidepressants, antihypertensives, CNS stimulants, narcotics

B. Dental Causes of oral malodor
-Gingivitis, periodontitis, gross carious lesions, subgingival/tongue plaque, tonsilloliths
-Bacteria include Treponema denticola, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythensis, Porphyromonas endodontalis, and Eubacterium species

II. TESTING FOR ORAL MALODOR

A.Organoleptic Testing – sniff or smell patient's mouth and nose air-scale 0-5
B. Halimeter by InterScan (Chatsworth, CA) is an "electronic nose" for VSCs

III. TREATMENT FOR ORAL DISEASES – TONGUE CLEANERS

A. Orafresh Tongue Blade – pediatric and adult sizes, Alwin Enterprises, 800.749-4553
B. Oolitt – bendable and low profile loop cleaners, Deep Trading Corp, 813.931.0390
C. Denteco – disposable razor-like, Denteco, Inc., 508.755.0804
D. Dr. Weider's – tung brush and gel, Peak Enterprises, www.tungbrush.com
E. Dr. Tung's – stainless steel arch/padded grippers or single handed, Dr.Tung's
F. Vista – disposable razor-like, Vista, Inc., 414.636.9755
G. Sakool – bendable plastic rod, U.S. Dentek Corp., 800.433.6835

IV. CHEMICAL PRODUCTS EFFECTIVE FOR ORAL MALODOR REDUCTION

A. Zinc Salts (chloride, citrate, acetate) – sustained breath odor reduction for 3 hours

   a. Toothpastes – TriOral, Listerine Tartar Control, Viadent Advanced Care, Aim TC, Close-Up TC, Kiss My Face Tartar Control, Smart Mouth Toothpaste
   b. Mouthwashes – Lavoris, Listermint, Listerine Tartar Control

B. Chlorine Dioxide (sodium chlorite) – sustained breath odor reduction for 5 hours

   a. Toothpastes – Oxyfresh, CloySys II, Therabreath, Profresh,
   b. Mouthwashes – Oxyfresh, CloSys II, Therabreath, Enfresh, Profresh

C. Essential Oils of Listerine (menthol, thymol, eucalyptol) – sustained breath odor reduction for 3 hours
   a. Toothpastes – Listerine EC paste and gel, Breath-So-Fresh Toothpaste
   b. Mouthwash – Listerine EC Mouthwash, many store brands,

D. Combinations of two of the above effective ingredients

   a. Smart Mouth – chlorine dioxide and zinc chloride mouthwash www.smartmouth.com
   b. Breath-So-Fresh – essential oils and zinc chloride
   c. Oxyfresh with Zinc – chlorine dioxide and zinc chloride www.badbreathcenter.com

V. Product Lines Promoted for Halitosis Treatment

CHEMICAL	MANUFACTURER	PRODUCT LINE/CHARACTERISTICS
COMBINATIONS		
1.) Chlorine Dioxide & Zinc		
TheraBreath	TheraBreath Global www.therabreath.com	Toothpaste, Oral Rinse, Breath Strips, Chewing Gum, Zox Mints, Mouth Sprays
Oxyfresh	Oxyfresh Worldwide Inc. www.oxyfreshww.com	Toothpaste-Flouride/Non-Flouride, Mouth rinse, Dental Gel, Breath Mints, Tongue Scraper, Relief Gel
Breeze	BreezeCare www.breezecare.com	Toothpaste, Breath Strips, Mouthrinse
KFORCE	BreezeCare	Pre-Rinse, Mouthwash, Lozenges
ProFresh	ProFresh www.profresh.com	Mouthwash-0.003%
CloSYSII	Rowpar Pharmaceuticals Inc. www.rowpar.com	Toothpaste, Oral Spray, Oral Rinse
EnFresh	www.enfresh.com	"Trizox" compound, Tongue gel, tongue brush, mouth rinse
BreathGel	International Dental Design Specialist, Inc.	'ZyClor' compound, tongue cleaner, mouth rinse
TriOral Fresh Breath SmartMouth Retail	TriOral www.trioral.com www.smartmouth.com	Mouthrinse in two chambered bottle. The green side is zinc and the white side is chlorine dioxide. Now 3 different rinses, travel packets and toothpaste (zinc only).
2.) Zinc Compounds		
BreathRx (CPC and Zinc rinse, zinc toothpaste)	Philips acquired Discus Dental www.philipsoralhealthcare.com	Mouthwash,toothpaste,gumballs,mints,spray and tongue cleaner
Arm & Hammer P.M.	Church & Dwight Co.	Toothpaste
TriOral Action	TriOral	Toothpaste, Gum, Mints
3.) Essential Oils		
Listerine	Johnson and Johnson www.listerine.com	Toothpaste, Mouthwash, PocketPaks Pocket Mist, Breath Strips
TheraBreath	TheraBreath Global	Rinse,Breath Strips,Gum,Toothpaste,Kit, even a kit to treat tonsil stones
5.) Naturals/Herbals		
Good Breath	Scandinavian Formulas	Soft Gel Tablets
Healthy Teeth and Gums	The Natural Dentist www.thenaturaldentist.com	Toothpaste, Oral rinse
Tooth & Gum Tonic	Dental Herb Company	Oral rinse, dentifrice
Tom's Natural	Tom's of Maine	Mouth rinse, toothpaste
Desert Essence Tea Tree Oil	Country Life	Mouth spray, tea tree ingredient found also found in toothpaste, mouthwash

V. STEPWISE APPROACH TO TREATMENT OF ORAL MALODOR

A. Good subgingival plaque control and twice daily tongue cleaning – NOT BRUSHING!!
B. Add zinc toothpaste twice daily. Increase zinc use with mouthwash as needed
C. Switch mouthwash to chlorine dioxide if response is not adequate to B or if taste disturbances are problematic for the patient.
D. Switch to chlorine dioxide toothpaste and a combination of chlorine dioxide and zinc mouthwash if C is not adequate. Maintain twice daily tongue cleaning prior to rinsing with deodorant/antimicrobial chemicals to enhance binding and efficacy.

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 hours 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 (all macrolides)	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(excluding azithromycin)	Ergotamine	Acute ergotamine toxicity. Use cautiously
	Methylprednisolone	Steroid clearance may be decreased. Caution.
	Penicillins	possible antagonism. Avoid static with cidal
	Pimozide (Orap)	Avoid all macrolides-risk of sudden death
	SSRIs (citalopram, escitalopram,fluoxetine, Sertraline, vilazodone)	AVOID CONCURRENT USE MACROLIDES DECREASE METABOLISM OF LISTED SSRIS.MONITOR..
	"**Statins" (except fluva-,pitava-prava)**	**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 prolong QT interval		
All Agents:	Antacids	Decreased quinolone absorption. AVOID
Ciprofloxacin (Cipro,g))	(iron, sucralfate, zinc)	CONCURRENT USE.
Levofloxacin (Levaquin)	Anticoagulants (Coumadin, g)	Increased risk of bleeding disorders. Monitor
Moxafloxacin (Avelox)		INR.
Ofloxacin (Floxin)	Antineoplastics	Quinolone serum levels may be decreased.
	Cimetidine (Tagamet, g)	Quinolone serum levels may be increased.
	Cyclosporine (Sandimmune, Neoral)	Cyclosporine renal toxicity may be enhanced.
	NSAIDs	Enhanced CNS stimulation
	Probenecid (Benemid, g)	Quinolone serum level may be increased50%.
	Theophylline	Increased theophylline toxicity possible with
Ciprofloxacin	Caffeine	Cipro and other. Consult MD Increased caffeine effects are possible.

ANTIFUNGALS	Anticoagulants (Coumadin)	Increased risk of bleeding disorders in anticoagulated patient. Consult MD.
Systemic Azole Agents (fluconazole, itraconazole, ketoconazole): all agents prolong QT interval		
	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.
	"Statins" (except fluva-,pitava-prava.)	Increased levels and SE of statins.
	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.
	Citalopram (Celexa,g)	**QT interval prolongation.AVOID COMBO.**
	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,edoxaban,,rivaroxaban,warfarin)**	**Increase risk of bleeding disorders in anticoagulated patient. AVOID COMBO**
	Antihypertensives (all but CCBs)	Decreased antihypertensive effect. Monitor Blood Pressure.
	(ACEI,B-blockers, diuretics)	
	Cimetidine (Tagamet, g)	NSAID levels increased/decreased
	Cyclosporine (Neoral, Sandimmune)	Nephrotoxicity of both agents may be increased. Avoid if possible.
	Combo of ACEor ARB & Diuretic	**30% increase in risk of kidney injury-called the TRIPLE WHAMMY on the kidney!**
	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 ()	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.
	Lybalvi (olanzepine/samidorphan)	**Samidorphan is an opioid antagonist so d/c 7 days prior to use of opioid analgesic**
Codeine (Hydrocodone lesser extent)	$2D_6$ 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)/Fentanyl/All Fentanyl derivatives	**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.
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.
	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,
	Citalopram (Celexa,g)	Increased risk of serotonin syndrome
	Diazepam	With high dose fentanyl gives CV depression.
	Droperidol (Inapsine)	Hypotension < pulmonary arterial pressure.
	MAOIs and furazolidone (Furoxone)	**Risk of hypertensive crisis.AVOID COMBO**
	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. Typel :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.
	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.

What is Torsades de Pointes (TdP)?

- TdP or "twisting of the points" refers to a polymorphic ventricular tachycardia.
- It is associated with a prolonged QT_c interval and bradycardia; patients may also report shortness of breath or syncope.
- TdP is thought to be caused by early after-depolarizations during prolonged repolarization.[1]
- It is often self-limiting but may be **potentially fatal**, sometimes leading to syncope and/or sudden death.
- TdP can be 1° (congenital) or 2° (acquired) due to metabolic disturbances, medical conditions, or (**most commonly**) drugs.[1]
- Some USA black box **FDA WARNINGS** due to QT prolongation: amiodarone, cisapride, droperidol, itraconazole & thioridazine.[13]
- Drug **FDA REMOVALS** due to QT prolongation: astemizole HISMANAL, grepafloxacin RAXAR & terfenadine SELDANE.[13]

Who is at risk?[1-6,14] - may use scoring system e.g. Pro-QTc score,[17] Tisdale Risk Score[18], 1-2-3-LQTS-Risk [19]

- The "**multiple hit**" theory suggests that a culmination of several factors is required to induce TdP.[2]
- Generally, these factors promote early after-depolarizations or prolongation of the action potential.[1]

Table 1: Risk Factors for QT interval Prolongation and TdP [1-6,14] greatest significance highlighted in yellow

Cardiac underlying conditions	**Metabolic**	**Other**
Bradycardia < 50 bpm	Altered nutritional status:	**Age** - ↑ risk with ↑ **age**
Cardiomyopathy:	Alcoholism	Cerebrovascular disease
Heart failure	**Anorexia**, starvation	**Female sex** –sex hormones regulate channel expression
Left ventricular hypertrophy	Diabetes	**Herbs**: e.g. aloe, echinacea, gingko, ginseng, licorice, St Johns wort
Myocardial infarction	Electrolyte disturbances:	**Hypothyroidism**
Congenital long QT interval	**Hypokalemia**	Obesity Pacritinib, Vernakalant, Fexinidazole
(incidence ~ 1/2500)[8]	**Hypomagnesemia** e.g. PPI's	Pituitary insufficiency; Male hypogonadism
Hypertension	Hypocalcemia	Poisoning –arsenic, organophosphates, nerve gas
Ischemic heart disease	Hypoglycemia	**Renal** & Liver disease
	Hypothermia	**DRUGS (see Table 2), esp. at high-dose & if IV**

Which drugs are implicated?

- Many **drugs** from a variety of therapeutic classes have been associated with **QT interval prolongation** and/or TdP **(see table)**.
- All of these drugs have in common their ability to block the I(kr) potassium channel; this results in ↑ repolarization time & a prolonged QT interval (beginning of QRS complex to end of T wave) on ECG.[1] Inward Na^+ & Ca^{++} influx channels may be affected.[8]
- Prolongation of the QT interval is thought to be **dose-related** and can occur within therapeutic range for some agents (e.g. amiodarone) but only at supra-therapeutic concentrations for others (e.g. clarithromycin).
- Different drugs can be **additive**. (Besides QT/DI's effects, a metabolic effect may be important e.g. ↓K^+⇒ **diuretics, laxatives**).
- Watch for drug interactions increasing risk of QT prolongation - see column on Cytochrome P450 Inhibitors.

How to avoid trouble:[2,6] Beware of common warning symptoms: dizziness, palpitations & syncope.

- **Identify those at risk** (Table 1); be aware however, that individuals' vulnerability can vary greatly due to a complexity of genetic and environmental factors which are not completely understood. Check family hx for syncope!
- **For patients with major or multiple risk factors, obtain a baseline ECG** and determine the QTc interval [corrected for heart rate (caution: correction less accurate with very fast or slow heart rates) – equation described elsewhere[7]].
- Long QTc interval is > 470msec for postpubertal males & > 480msec for postpubertal females.

Short QTc ≤ 410 msec ..... VERY LOW RISK[2]

-may not require ECG monitoring after initiating a QT-prolonging agent. Start monitoring if additional risk factors develop or if a drug interaction is likely.

Intermediate QTc 411-449 msec ..... LOW to MODERATE RISK

- repeat ECG after initiating any QT-prolonging agent, again at steady state, weekly for 1st month, then q6months and when any other QT-prolonging agent is added or if a drug interaction is likely.
- if QTc ≥ 450 msec, reduce dosages or avoid these agents and use alternatives.

Prolonged QTc ≥ 450 msec ..... MODERATE to HIGH RISK

- repeat ECG after initiating any QT-prolonging agent, again at steady state, weekly for 1st month, then q6months and when any other QT-prolonging agent is added or if a drug interaction is likely
- if **QTc > 500 msec or > 60 msec over baseline avoid** these agents and use alternatives
- regular **monitoring of serum K+ and Mg++** also advised

Rule of thumb:[8]

A QTc change of < 10 msec is acceptable as long as there are no other significant risk factors.
If the QTc change is > 10 msec, reduce dosage or eliminate the drug(s), monitor more closely.

How to treat TdP:

Emergency:[9] *Do not use standard antiarrhythmics.*

- Give **magnesium** sulphate 2g IV over 2min. If ineffective, consider isoproterenol, dobutamine, or atropine IV.
- Consider potassium if serum K+ is low; bicarbonate for TCP (phencyclidine) or quinidine poisoning.
- Lidocaine & phenytoin have also been used; alternatives are cardiac pacing & isoproterenol.
- **Later:** Stop the offending agent. Maintain normal K^+, Mg^{++}, HCO_3^-. Keep out of trouble as above.

Table 2: Drugs which can prolong QT Interval [1,3,6,9,12,13,14] - see www.torsades.org / www.crediblemeds.org

Cardiovascular

Anti-arrhythmics
Amiodarone (low risk of TdP compared to other class III agents such as sotalol; however potential for DIs)
Bepridil
Bretylium
Diltiazem
Disopyramide
Dofetilide
Dronedarone
Flecainide
Hydroquinidine
Ibutilide
Mexiletine
Nifekalant
Procainamide
Propafenone
Quinidine less at ↑ dose
Sotalol 0.3% at 80mg/day, 3.8% at > 680mg/day
Vernakalant

Dobutamine
Dopamine
Isradipine
Nicardipine
Norepinephrine
Ranolazine

Caution: COMBINATIONS of PHENOTHIAZINES with TCAs, BETA BLOCKERS, & ANTICONVULSANTS since ↑ QT risk especially if ↑↑ risk factors present.

CNS / Psychotropic

ADHD agents
Amphetamine
Atomoxetine
Dextroamphetamine
Guanfacine
Lisdexamfetamine
Dex- & Methylphenidate
Serdexmethylphenidate

Antipsychotics
Amisulpride, Asenapine, **Aripiprazole,** Benperidol, **Brexpiprazole**
Butyrophenones
Haloperidol esp. if ↑ dose or IV
Chlorprothixene,Clotiapine
Clozapine, Flupentixol, Iloperidone, **Levosulpiride,** Lumateperone, Lurasidone
Paliperidone,
Phenothiazines
Chlorpromazine
Mesoridazine
Methotrimeprazine
Perphenazine
Thioridazine
Pimavanserin
Pimozide
Quetiapine
Risperidone
Sertindole, Sultopride
Tiapride
Ziprasidone, Zotepine
Zuclopenthixol

Anticonvulsants
Felbamate
Lithium

SSRIs
Citalopram >40mg/d; >20mg in elderly
Escitalopram if >20mg/day, or >10mg in elderly
Fluoxetine
Fluvoxamine
Paroxetine (esp. ↑ pimozide)
Sertraline-concentration dependent
Trazodone

Gepirone

SNRI
Des & -venlafaxine
Mirtazapine

TCAs
Amitriptyline
Amoxapine -seems ok
Clomipramine
Desipramine
Doxepin
Imipramine
Maprotiline
Nortriptyline
Protripyline -seems ok
Trimipramine
Moclobemide

Mianserin

Anti-Infective

Antibiotics
Cotrimoxazole
Fluoroquinolones
Ciprofloxacin mainly through DI on a ↑QT drug, but some direct QT effect
Gatifloxacin
Gemifloxacin
Garenoxacin
Levofloxacin
Moxifloxacin
Nemonoxacin
Norfloxacin
Ofloxacin
Sparfloxacin
Lefamulin
? Linezolid
Macrolides
Azithromycin
Clarithromycin
Erythromycin[11]
Roxithromycin
Telavancin
Telithromycin

Azole Antifungals
Fluconazole
Itraconazole
Levoketoconazole
Ketoconazole
Posaconazole
Voriconazole

Antimalarials
Artemether/lumefantrine
Chloroquine
Halofantrine
Hydroxychloroquine
Mefloquine
Piperaquine
Primaquine
Quinine
Pentamidine

Metronidazole

Top 3 suspected drugs:
1) **sotalol** 66% (58/88) 2) **digoxin** 11% (10/88)
3) **citalopram** 10% (9/88)
[**Swedish ADR Registry 2008**: n=61,788 ADRs, n=88 torsades (0.14%)][15]

Drugs removed from USA due to QT: astemizole, cisapride, grepafloxacin, levomethadyl, probucol, & terfenadine.

Miscellaneous

Abarelix, Abiraterone acetate , **Aclarubicin**, Alfuzosin, Alimemazine, Alpelisib, Amantidine, Amphotericin B, Amsacrine, Anagrelide, Apalutamide, Apomorpine, **Arsenic** trioxide, Asciminib, Atazanavir, Bedaquiline, Bendrofluazide, Betrixaban, Bicalutamide,Bosutinib, Brigatinib, Buprenorphine, Cabozantinib, Caffeine, Capecitabine, Carbetocin, **Ceritinib, Cesium chloride**, Chloral hydrate, Cilostazol, Cinacalcet, **Cisapride** (special access), Clofazimine, **Cocaine**, Cobimetinib, Crizotinib, Cyclosporine, Dasatinib, Degarelix, Delamanid, Dexmedetomidine, Dextromethorphan+ Quinidine, **Donepezil**, Efavirenz, Eliglustat, Encorafenib, Energy drinks, entrectinib, Enzalutamide, Eperisone, Epirubicin, Eribulin, Etrasimod, Ezogabine, Fenspiride, Fexinidazole, Fingolimod, Fluorouracil, Foscarnet, Galantamine, Ginseng, Gilteritinib , Glasdegib, Gilteritinib, Givinostat, Goserelin, Grapefruit juice ~ 1 liter, Histrelin, Hydrocodone ER, **Hydroxyzine**, Ibogaine, Imatinib, Indapamide, ?Inotuzumab ozogamicin, Isoflurane, **Ivabradine**, Ivosidenib, Kaletra, Ketanserin, Lacidipine, Lapatinib, Lenvatinib, Leuprolide, Levetiracetam, **Levmetamfetamine,** Levomethadone, Levomethadyl, Loperamide: abuse or DI's, Lopinavir/Ritonavir, Lofexidine, Macimorelin, **Meglumine antimoniate, Methadone,** Metolazone, Midodrine, Midostaurin, Mifepristone, Mirabegron, **Mobocertinib** , Motixafortide, Necitumumab, Nilotinib, Nusinersen, Octreotide, Oliceridine, Orphenadrine, Osilodrostat, Osimertinib, **Oxaliplatin**, Oxytocin, Oxycodone, Oxymetazoline, Ozanimod, Pacritinib, Panobinostat, **Papaverine IV**, Pasireotide, Pazopanib, Phenylephrine, Pilsicainide, Pitolisant, Ponesimod, Pretomanid, **Probucol**, **Propofol**, **Propoxyphene**, Pseudoephedrine, Pralsetinib, Prothipendyl, **Quizartinib**, Relugolix, Remdesivir, Remimazolam, Ribociclib, Rilpivirine ≥75mg/d, Ritodrine, Rivastigmine, Romidepsin, Rucaparib, **Saquinavir**, Selpercatinib, **Sevoflurane**, Sibutramine, Siponimod, Solifenacin, Sorafenib, Sunitinib, Tacrolimus, Tamoxifen, Tazemetostat, Tebentafusp, Telaprevir, **Terodiline**, Tizanidine, Tolterodine, Torsemide, **Tramadol**, **Triclabendazole, Trifluridine,** Triptans recently off QT list, Triptorelin, Valbenazine, **Vandetanib**, Vardenafil, **Vemurafenib**, Voclosporin & Xylometazoline.

Antiemetics
Dolasetron esp if IV
Domperidone esp if IV, >30mg orally/day or with ketoconazole/3A4 inhibitors
Droperidol more if ≥ 1.25mg
Granisetron, Metoclopramide
Ondansetron esp ≥ 32mg **IV**, avoid over 8mg if ≥75yr ; >16mg if <75yr
Palonosetron; Promethazine
Tropisetron

Appetite suppressant
Benzphetamine, **Diethylpropion**, Ephedrine, Fenfluramine, **Phendimetrazine**, Phentermine, Sibutramine

Antihistamines
Bilastine, Diphenhydramine Clemastine, Loratidine (but no reports), Rupatadine.
Withdrawn: Astemizole, Terfenadine

Bronchodilators
Epinephrine, Fenoterol, Indacaterol, Isoproterenol, Levalbuterol, Metaproterenol, **Olodaterol,** Salbutamol/Albuterol, Salmeterol, Terbutaline, **Vilanterol** minimal at 100mcg

Cytochrome P450 Inhibitors (DIs)

- Since many QT-prolonging agents are metabolized by the **cytochrome P450 system**, serious and sometimes lethal drug interactions can occur when combined with drugs which **inhibit** or compete for binding to these isoenzymes.
- **Some drugs** (eg. erythromycin & amiodarone) **prolong the QT Interval AND act as inhibitors to potentially increase levels or QT effects of concomitant medications.**

CYP3A4 Inhibitors
Amiodarone; Azole antifungals (e.g. Flu-, Itra-, & Keto-conazole); **Calcium channel blockers** (Diltiazem, Verapamil); Cimetidine; **Ciprofloxacin;** Grapefruit juice; **HIV protease inhibitors; Macrolides** (**Clarithromycin**, **Erythromycin**, Troleandomycin, NOT Azithromycin); Methadone; Telithromycin; **SSRIs** (Fluoxetine, Fluvoxamine, Norfluoxetine, Nefazodone, **Paroxetine**); Trazodone

CYP2D6 Inhibitors
Beta Blockers, Haloperidol, Phenothiazines, Quinidine, SSRIs (NOT citalopram), Terbinafine, TCAs

CYP1A2 Inhibitors (less significant)
Fluoroquinolones, Fluvoxamine, Grapefruit juice

Miscellaneous:
Piperacillin/tazobactam may ↓ K^+ ⇒ QT risk.
PPI's (eg. omeprazole) may ↓magnesium⇒ QT risk.

BOLD=major significance (well-documented) REGULAR=low-moderate significance (fewer case reports) *ITALIC=minor significance (theoretical, few if any case reports)*

{**Long QT syndrome**: a familial condition associated with recurrent syncope & sudden cardiac death resulting from ventricular arrhythmias; may be misdiagnosed as epilepsy. Triggers for arrhythmias: meds that prolong the QT interval or subtype specific factors such as swimming & other exercise (long QT1), auditory stimuli & emotional stress (long QT2), & rest or sleep (long QT3 ? mexiletine benefit). **β-blockers** (**nadolol**, propranolol) are usually effective; **implantable cardioverter defibrillators** reserved for people deemed at high risk or refractory to medical treatment. Thoracoscopic left cardiac sympathectomy an option - highly effective & useful if β-blockers not tolerated or an implantable cardioverter defibrillator is contraindicated.} Abrams 2010