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®)

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Direct Oral Anticoagulation (DOAC) Monitoring Checklist for Pharmacists

This is a tool to support ongoing follow-up, monitoring, and adherence support of patients receiving a direct oral anticoagulant (apixaban, dabigatran, edoxaban, rivaroxaban) at the point of referral. This tool is NOT for initial prescriptions.

Place pharmacy label here
- Patient name, DOB (patient identifier)
- Date of assessment
- Assessment done by (pharmacist initials)
- Date of last refill

PATIENT INFORMATION

INDICATION	APIXABAN	DABIGATRAN	EDOXABAN	RIVAROXABAN
☐ Atrial Fibrillation	☐ 5 mg bid ☐ 2.5 mg bid	☐ 150 mg bid ☐ 110 mg bid	☐ 60 mg daily ☐ 30 mg daily	☐ 20 mg daily ☐ 15 mg daily
☐ Venous Thromboembolism	☐ 10 mg bid x 7 days, then 5 mg bid x 3 months minimum, then as per MD ☐ 2.5 mg bid for recurrent VTE prevention after at least 6 months of treatment dose	Parenteral treatment x 5 – 10 days, then ☐ 150 mg bid (or ☐ 110 mg bid) x 3 months minimum, then as per MD	Parenteral treatment x 5 – 10 days, then ☐ 60 mg daily (or ☐ 30 mg daily) x 3 months minimum, then as per MD	☐ 15 mg bid x 21 days, then 20 mg daily x 3 months minimum, then as per MD ☐ 10 mg daily or ☐ 20 mg daily for recurrent VTE prevention after at least 6 months of treatment dose

Date of original VTE Rx: If > 3 months ago, confirm intended duration:

HEALTH STATUS SINCE LAST REFILL		ACTUAL OR POTENTIAL DTP?/OTHER COMMENTS
Any new medical problems/ED visits/procedures since last refill? *(If yes, describe in margin)*	☐ Y ☐ N	
Any planned medical procedures and/or surgeries? *(If yes, describe in margin)*	☐ Y ☐ N	
ADHERENCE WITH DOAC THERAPY		**ACTUAL OR POTENTIAL DTP?/OTHER COMMENTS**
Is this refill outside of the usual interval?	☐ Y ☐ N	
Is the patient responsible for their own medication administration?	☐ Y ☐ N	
If no, who is responsible?		
Has the patient reported missing 1 or more doses in a week? *(*explore reasons in margin)*	☐ Y ☐ N	
If yes, number of missed doses:		
Patient taking the medication properly? (i.e. rivaroxaban with food, don't open dabigatran, etc.)	☐ Y ☐ N	
BLEEDING & RISK FACTORS FOR BLEEDING		**ACTUAL OR POTENTIAL DTP?/OTHER COMMENTS**
Any bleeding episodes since the last refill?	☐ Y ☐ N	
Latest hemoglobin *(if available)*: g/L Date :		
Has there been a decrease in hemoglobin? ☐ NA	☐ Y ☐ N	
Patient consumes more than 7 alcoholic drinks per week?	☐ Y ☐ N	
Patient has experienced a fall since the last refill? *(*if yes, refer for walking aid assessment)*	☐ Y ☐ N	
Systolic blood pressure uncontrolled (SBP>160mmHg) ☐ NA	☐ Y ☐ N	
CREATININE CLEARANCE/RENAL FUNCTION		**ACTUAL OR POTENTIAL DTP?/OTHER COMMENTS**
Patient aware of any concerns/issues with renal function?	☐ Y ☐ N	
Medication change that may indicate a change in renal function?	☐ Y ☐ N	
Recent dehydrating illness *(i.e. vomiting, diarrhea)*?	☐ Y ☐ N	
Weight: kg Nephrologist on file?	☐ Y ☐ N	
Latest eGFR: mL/min ☐ NA Creatinine : µmol/L ☐ NA		
If eGFR less than 50 mL/min, calculate CrCl mL/min		
Does the current does require adjustment for renal function? *(*see dosing chart on back)*	☐ Y ☐ N	
DRUG INTERACTION		**ACTUAL OR POTENTIAL DTP?/OTHER COMMENTS**
Any antiplatelets?	☐ Y ☐ N	
☐ ASA ☐ Clopidogrel ☐ Prasugrel ☐ Ticagrelor ☐ Other		
Taking NSAID?	☐ Y ☐ N	
Other medications that can affect DOAC levels? *(*If yes, please describe in margin)*	☐ Y ☐ N	
EXAMINATION/ASSESSMENT		**ACTUAL OR POTENTIAL DTP?/OTHER COMMENTS**
Blood pressure under control? ☐ NA	☐ Y ☐ N	
Blood pressure today? mm Hg ☐ NA		
Any symptomatic hypotension? ☐ NA	☐ Y ☐ N	
FINAL ASSESSMENT		**ACTUAL OR POTENTIAL DTP?/OTHER COMMENTS**
☐ No issues identified		
☐ Actual DTP or potential DTP ☐ High dose ☐ Low dose ☐ Adherence difficulties ☐ Interactions ☐ Bleeding ☐ Other		

ACTION	OTHER COMMENTS
☐ Patient education ☐ Treatment recommendations *(i.e. Pharmaceutical opinion)* ☐ Referral ☐ Other *(*please describe in margin)* ☐ I have counselled on the importance of adherence, handling of missed doses, proper administration, avoidance of OTC ASA and NSAIDs, minimizing EtOH and self monitoring.	

NA = information not available

RPh SIGNATURE : _____

Updated: July 13, 2018 • This checklist was developed for pharmacists by Leblanc K, Gladstone DJ, Snow B, Mandlsohn L, Papastergiou J, Semchuk B, Kapoor V, Guirguis L, as an investigator-initiated academic project. It was supported by Thrombosis Canada through an unrestricted grant from Bayer Canada Inc. • It was adapted from: Gladstone DJ, Geerts WH, Douketis J, Ivers N, Healey JS, Leblanc K. Ann Int Med. 2015;163:382-386. The sponsors had no role in the checklist development or content.

INDICATION	DOSING OF DIRECT ORAL ANTICOAGULANTS (DOACs)		*Adapted from the AFIB Innovation Program (www.afibinnovationprogram.com)*
	Oral Anticoagulant	**Usual Dose**	**Adjusted Dose**
Atrial Fibrillation	**Apixaban (Eliquis®)** (Direct Factor Xa Inhibitor)	5 mg BID	2.5 mg BID Recommended in patients with 2 of the following: age ≥ 80 yrs, body weight ≤ 60 kg, or serum creatinine ≥ 133 µmol/L No dose recommendation can be made if CrCl between 15 and 24 mL/min Avoid in patients with CrCl less than 15 mL/min
	Dabigatran (Pradaxa®) (Direct Thrombin [IIa] inhibitor)	150 mg BID	110 mg BID Recommended in patients age ≥ 80 yrs or those age ≥ 75 yrs with at least one other bleeding risk factor (i.e. CrCl 30–50 mL/min, concomitant ASA/NSAID, interacting drug, blood dyscrasia, recent bleed etc.) Avoid in patients with CrCl less than 30 mL/min
	Edoxaban (Lixiana®) (Direct Factor Xa inhibitor)	60 mg daily	30 mg daily Recommended in patients with 1 or more of the following: CrCl 15–50 mL/min, body weight 60 kg or less, or concomitant use of P-gp inhibitors EXCEPT amiodarone and verapamil Avoid in patients with CrCl less than 15 mL/min
	Rivaroxaban (Xarelto®) (Direct Factor Xa inhibitor)	20 mg daily	15 mg daily Recommended in patients with moderate renal impairment (CrCl 15–49 mL/min) or in combination with a P2Y12 inhibitor in patients who undergo angioplasty with stent placement (max 12 months) Avoid in patients with CrCl less than 15 mL/min. Use with caution if CrCl 15-29 mL/min
Venous Thromboembolism	**Apixaban (Eliquis®)** (Direct Factor Xa Inhibitor)	10 mg BID x 7 days, then 5 mg BID x 3 months minimum 2.5 mg bid may be used for prevention of recurrent VTE after at least 6 months of standard treatment	No dose adjustment if CrCl 30 mL/min or more; use with caution if CrCl between 15 and 29 mL/min; avoid if CrCl less than 15 mL/min
	Dabigatran (Pradaxa®) (Direct Thrombin [IIa] inhibitor)	Parenteral treatment x 5–10 days, then 150 mg BID x 3 months minimum	110 mg BID Recommended in patients age ≥ 80 yrs or those age ≥ 75 yrs with at least one other bleeding risk factor. Avoid in patients with CrCl less than 15 mL/min; use with caution if CrCl 15–29 mL/min
	Edoxaban (Lixiana®) (Direct Factor Xa inhibitor)	Parenteral treatment x 5–10 days, then 60 mg daily x 3 months minimum	30 mg daily Recommended in patients with 1 or more of the following: CrCl 15–50 mL/min, body weight 60 kg or less, or concomitant use of P-gp inhibitors EXCEPT amiodarone and verapamil Avoid in patients with CrCl less than 15 mL/min
	Rivaroxaban (Xarelto®) (Direct Factor Xa inhibitor)	15 mg BID x 21 days, then 20 mg daily x 3 months minimum 10 mg OR 20 mg daily may be used for prevention of recurrent VTE after at least 6 months of standard treatment	No dose adjustment if CrCl 15 mL/min or more; use with caution if CrCl 15–29 mL/min; avoid if CrCl less than 15 mL/min

ADMINISTRATION INFORMATION	*1.Song Y, et al. Clinical Pharmacology and Therapeutics. 2003;93(Suppl 1):S120-1; 2.Moore KT, et al. Clinical Pharmacology in Drug Development. 2004;3(4):321-7*
Apixaban (Eliquis®)	• May be taken twice daily without regard to meals/food • For NG Administration, may be crushed and suspended in 60 mL water[1]
Dabigatran (Pradaxa®)	• Must not crush, chew or open capsules (increases exposure by almost double (1.8 times)) • Must be stored in original packaging (foil or bulk bottle) as light, moisture can cause product breakdown
Edoxaban (Lixiana®)	• May be taken once daily without regard to meals/food
Rivaroxaban (Xarelto®)	• Doses of 15–20 mg must be taken with food (AUC increases 39%, Cmax increases 75% with food) • For NG Administration, may be crushed and suspended in 50 mL water; follow immediately with food (enteral feeds); ensure NG tube not distal to stomach or decreased absorption can occur[2]

DRUG INTERACTIONS THAT MAY AFFECT DOAC DRUG LEVELS

Potential ↑ in Apixaban		Potential ↓ in Apixaban	Potential ↑ in Dabigatran		Potential ↓ in Dabigatran	
*Diltiazem**	*Naproxen**	*Carbamazepine¥*	*Amiodarone**	*Quinidine*§*	*Antacids§*	*Strong P-glycoprotein inducers‡*
Ketoconazole, itraconazole, voriconazole, posaconazole = azole-antimycotics‡	*Ritonavir (all HIV protease inhibitors)‡*	*Phenobarbital¥*	*Clarithromycin**	*Ritonavir**	*Atorvastatin***	
	Strong inhibitors of both P-glycoprotein and CYP 3A4‡	*Phenytoin¥*	*Cyclosporine**	*Saquinavir**	*Carbamazepine¥*	*Phenytoin¥*
		Rifampin¥	*Dronedarone¥*	*Tacrolimus**	*Proton Pump Inhibitors**	
		St. John's Wort¥	*Itraconazole**	*Tipranavir¥*	*Rifampin¥*	
		Strong inducers of both P-glycoprotein and CYP-3A4¥	*Ketoconazole‡*	*Ticagrelor¥*	*St. John's Wort¥*	
			*Nelfinavir**	*Verapamil*§*	*Tenofovir¥*	
			*Posaconazole**	*Strong P-glycoprotein inhibitors‡*		

Potential ↑ in Edoxaban		Potential ↓ in Edoxaban	Potential ↑ in Rivaroxaban		Potential ↓ in Rivaroxaban	
*Amiodarone**	*Ketoconazole£*	*Atorvastatin**	*Clarithromycin**	*Posaconazole‡*	*Carbamazepine¥*	*Strong inducers of both P-glycoprotein and CYP 3A4¥*
Cyclosporine£	*Quinidine£*	*Carbamazepine¥*	*Erythromycin**	*Ritonavir‡*	*Phenobarbital¥*	
*Digoxin**	*Verapamil**	*Esomeprazole**	*Fluconazole**	*Strong inhibitors of both P-glycoprotein and CYP 3A4‡*	*Phenytoin¥*	
Dronedarone£	*Protease Inhibitors¥*	*Phenobarbital¥*	*Ketoconazole‡*		*Rifampin¥*	
Erythromycin£		*Phenytoin¥*	*Itraconazole‡*		*St. John's Wort¥*	
		Rifampicin¥				

Note that drug interaction data with the DOACs is limited and this table reflects currently available data. Consider Pharmacist consult as needed. Dabigatran etexilate and edoxaban are substrates for the P-glycoprotein transporter (P-gp) and as such any strong inhibitors or inducers should be avoided. Rivaroxaban and apixaban are eliminated by both P-gp and cytochrome P-450 3A4 (CYP-450 3A4). As such the concomitant use of strong inhibitors and inducers of both P-gp and 3A4 should be avoided.

**no empiric dosage adjustment required, however use with caution, § recommend to give 2 hours after dabigatran, ‡contraindicated, ¥ caution advised if co-administering, should be avoided, £ reduce dose of edoxoban to 30 mg daily, **no dose adjustment is required*

PRE-OPERATIVE MANAGEMENT OF PATIENTS RECEIVING DIRECT ORAL ANTICOAGULANTS FOR ATRIAL FIBRILLATION

Drug (dose regimen)	Renal Function	Minor Surgery/Procedure (Low Bleeding Risk) 12–15% residual anticoagulant effect at time of surgery acceptable	Major Surgery/Procedure or Spinal Anesthesia (High Bleeding Risk) <10% residual anticoagulant effect at time of surgery acceptable
		For examples of low and high risk bleeding procedures visit: http://thrombosiscanada.ca/?page_id=502&calc=perioperativeAnticoagulantAlgorithm	
Apixaban (Eliquis®) (twice daily)			
$t_{1/2}$ = 9 hours	Normal renal function or mild impairment (CrCl > 30 mL/min)	Last dose: 2 days before surgery (skip 2 doses)	Last dose: 3 days before surgery (skip 4 doses)
Dabigatran (Pradaxa®) (twice daily)			
$t_{1/2}$ = 14 hours	Normal renal function or mild impairment (CrCl > 50 mL/min)	Last dose: 2 days before surgery (skip 2 doses)	Last dose: 3 days before surgery (skip 4 doses)
$t_{1/2}$ = 15–18 hours	Moderate renal impairment (CrCl 30 – 50 mL/min)	Last dose: 3 days before surgery (skip 4 doses)	Last dose: 4 to 5 days before surgery (skip 6–8 doses)
Edoxaban (Lixiana®) (once daily)			
$t_{1/2}$ = 10–14 hours	Normal renal function or mild impairment (CrCl ≥ 30 mL/min)	Last dose: 2 days before surgery (skip 1 dose)	Last dose: 3 days before surgery (skip 2 doses)
Rivaroxaban (Xarelto®) (once daily)			
$t_{1/2}$ = 9 hours	Normal renal function or mild impairment (CrCl > 30 mL/min)	Last dose: 2 days before surgery (skip 1 dose)	Last dose: 3 days before surgery (skip 2 doses)

This table provides general guidance and may not be applicable to all patients including those undergoing neuroaxial anaesthesia. Consultation with a specialist is advised for specific patient management, particularly in patients with an active thrombus such as those with VTE.

Adapted from www.thrombosiscanada.ca/wp-content/uploads/2014/05/Peri-operative-Management-of-Patients-who-are-Receiving-a-New-Oral-Anticoagulant-dabigatran-rivaroxaban-apixaban.pdf

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.

Xerostomia (Dry Mouth) Patient Handout

Department of Oral Pathology, Radiology and Medicine
The University of Iowa Colleges of Dentistry and Pharmacy
2024

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, daily 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. DentiCare Pro-Gel by Medicom is a 5000ppm neutral NaF gel with no flavors or dyes-use in trays

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.

QT Prolongation and Torsades de Pointes: Drugs and Sudden Death [20 CDN'2023]

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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, Mididorine, 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]

Drug Interactions: Overview [1,2,3,4]

A Crawley BSP, A Haines BSP, T Smart BSP © www.RxFiles.ca Sept 2024

- Drug interactions are responsible for 10-20% of the adverse drug reactions that cause hospitalizations. They are often multi-faceted, and **require clinical judgment** to manage appropriately.[2,5] A good understanding of interactions helps provide individualized drug therapy. *Alert fatigue* from computer DI warnings can contribute to missed interactions.
- Consider interactions when *starting* a drug, *adjusting* the dose of a drug, or *discontinuing* a drug.
- Older adults tend to be at higher risk of DIs (↓ liver function, ↓ kidney function, ↓ lean muscle mass, ↑ body fat, ↑ polypharmacy).
- Consult (>1) DI resources: **pharmacists**, product monographs, LexiComp, Micromedex, Natural Medicines Database, Stockley's, www.drugs.com, www.hiv-druginteractions.org, www.hep-druginteractions.org, www.crediblemeds.org, etc.

Alternatives with Fewer Interactions

A disclaimer: drug interactions are one of several considerations when selecting a medication. For example, citalopram has fewer cytochrome P450 (CYP) interactions than most other SSRIs. However, citalopram (at high doses) also prolongs the QT-interval more than some other SSRIs. Azithromycin has no CYP3A4 inhibition, giving it an advantage over clarithromycin. However, azithromycin is more likely than clarithromycin to create resistance in bacteria, due to its long half-life. Perfect drugs are hard to come by!

If prescribing ...	Consider: [see page 220 for interaction lists]
Lipid-lowering Agents	• **Fewer interactions**: rosuvastatin, pravastatin. • **More interactions**: atorva-, lova-, simva-statin → 3A4 substrates. Fluvastatin → inhibits 2C9. Gemfibrozil → inhibits 1A2, 2C19, 2C8, & 2C9. Can increase statin levels (increased risk of rhabdomyolysis). Cholestyramine → numerous absorption interactions. • **Note**: statins in general are first-line choices over fibrates or cholestyramine (due to hard outcome evidence). However if prescribing a fibrate, fenofibrate has much fewer DIs than gemfibrozil.
Oral Anticoagulants	• Warfarin has many more interactions than DOACs (apixaban, rivaroxaban, dabigatran, edoxaban). However, important to note that (1) very few interactions with warfarin are absolutely contraindicated – as warfarin dose can be adjusted in response to INR; (2) DOACs also have interactions (esp. **3A4** inducers/inhibitors, P-gp) & little guidance on management.
Hormonal contraceptives	• **Fewer interactions**: copper IUD → no drug interactions. • **More interactions**: combined hormonal contraceptives with CYP inducers → risk of contraceptive failure. Levonorgestrel IUD & depo-medroxyprogesterone with CYP inducers → less risk vs orals, but still may fail.
HIV medications	• **Fewer interactions**: NRTIs (e.g. lamivudine, emtricitabine, tenofovir), & INSTIs (especially raltegravir, bictegravir). • **More interactions**: NNRTIs (e.g. efavirenz, rilpivirine), protease inhibitors (e.g. atazanavir), PK boosters (i.e. ritonavir, cobicistat)
Opioids	• Methadone → many interactions: 2D6 inhibitor; 3A4 substrate; causes QT-prolongation. • Fentanyl patch → reports of 3A4 inhibitors causing drug accumulation / AE.[33] (12mcg patch useful to facilitate tapering)
Antidepressants	• **Fewer interactions**: sertraline, es-/citalopram, venlafaxine, vortioxetine (& see **RxFiles Antidepressants** page 177). • **More interactions**: many potent CYP inhibitors: bupropion (2D6 Θ), duloxetine (2D6 Θ), fluoxetine (2C19 Θ, 2D6 Θ), paroxetine (2D6 Θ), fluvoxamine (1A2 Θ, 2C19 Θ). St. John's Wort is a CYP inducer.
Anticonvulsants	• **Fewer interactions**: gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin. Note: anticonvulsants do not all have identical therapeutic uses; using an alternative agent may be inappropriate – check evidence/indication. • **More interactions**: carbamazepine, phenytoin, phenobarbital, primidone (potent CYP inducers).
Macrolides	• **Fewer interactions**: azithromycin (but overuse leads to resistance). • **More interactions**: clarithromycin, erythromycin → inhibits 3A4.
Acid-Reducing Agents	• **Fewer interactions**: ranitidine, famotidine, lansoprazole, pantoprazole, rabeprazole. • **More interactions**: Omeprazole, esomeprazole → inhibits 2C9 & 2C19. Ca^{++}, Mg^{++}, & Al^{+++} antacids → can bind to some meds. Cimetidine → inhibits 2C19 & 2D6.

Clinical Pearls

1. Always check for interactions when prescribing the following high risk medication classes: **anticonvulsants** (e.g. carbamazepine, phenobarb, phenytoin); **azole antifungals** (e.g. fluconazole); **HIV meds** (e.g. lopinavir, efavirenz); **hepatitis C meds** (e.g. ombitasvir, sofosbuvir); **immunosuppressants** (e.g. tacrolimus, cyclosporine); **amiodarone** or **dronedarone**; **methadone**; **digoxin**; **lithium**; **theophylline**; **warfarin**.
2. Antibiotics, despite short-term use, can cause clinically significant DIs. Four to watch out for are **cotrimoxazole**, **ciprofloxacin**, **clarithromycin**, and **erythromycin**. A few DIs that have led to hospital admissions in older adults:

cotrimoxazole	+	ACEIs, ARBs, NSAIDs, spironolactone	→	hyperkalemia
cotrimoxazole	+	glyburide	→	hypoglycemia
cotrimoxazole	+	warfarin	→	↑ bleed risk
clarithromycin	+	digoxin	→	digoxin toxicity

3. **Nitrates** must be spaced from PDE5Is (wait 24 hrs after **sildenafil** or **vardenafil**, & 48 hrs after **tadalafil**).
4. Avoid routinely adjusting a **warfarin** dose proactively when starting/stopping an interacting med. Check the INR in 4-6 days, and reactively adjust the warfarin dose.
5. Space calcium supplements from **levothyroxine** by at least 2 hrs, and considering holding calcium supplements while on oral **fluoroquinolones** (e.g. ciprofloxacin) or tetracyclines.
6. Avoid combining medications with opposing mechanisms, for example:
   - AChEIs (e.g. donepezil) + anticholinergics (e.g. amitriptyline)
   - dopamine agonists (e.g. levodopa) + dopamine antagonists (e.g. metoclopramide)
7. Grapefruit (CYP3A4 inhibitor) ↑ levels of atorva-, lova-, simva-statin.
   Likely no concern if: on a low statin dose (e.g. atorvastatin 10-20mg); taking grapefruit infrequently; on rosuvastatin or pravastatin.[29]
   If taking grapefruit regularly: use low dose atorva-, lova-, or simva-statin; or switch statins.
8. Temporarily hold atorva-, lova-, or simva-statin when clarithro- or erythro-mycin are prescribed for short-term infections.
9. Herbal products can cause DIs (e.g. garlic, gingko, or ginseng ↑bleeding with **warfarin**); routinely inquire. See **RxFiles Herbal DIs** page 221-222.
10. When reviewing patients **already on** an interacting combination, consider:
    (a) Do both meds have clear indications? **(b)** Is the patient clinically stable?
    (c) What are the risks/benefits of continuing the combination, and are safer options available?

Enzyme Inducers and Inhibitors - see pg 219

Common Inducers: **carbamazepine**, dexamethasone, efavirenz, **phenobarb**, **phenytoin**, rifabutin, **rifampin**, ritonavir, St. John's Wort

Common Inhibitors: amiodarone, atazanavir, **azole antifungals** (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole), **bupropion**, CCBs (diltiazem, verapamil), cimetidine, **ciprofloxacin**, cobicistat, **cotrimoxazole**, delavirdine, diphenhydramine, dronedarone, duloxetine, fluvastatin, gemfibrozil, **macrolides** (clarithromycin, erythromycin), mifepristone, **ritonavir** (part of **PAXLOVID**), **SSRIs** (esp. fluoxetine, fluvoxamine, paroxetine)

Enzyme induction results in increased drug metabolism → i.e. LOWER drug levels.
Enzyme inhibition results in decreased drug metabolism → i.e. HIGHER drug levels.
*Note: the opposite occurs with **prodrugs** ... since these have an active metabolite*

- Pay close attention when inducers/inhibitors are paired with HCV meds, HIV meds, anticonvulsants, immunosuppressants, amiodarone, dronedarone, methadone, digoxin, theophylline, warfarin → these interactions are often very significant & can easily cause patient harm.
- The effect of enzyme induction is often gradual (e.g. often >1 week before full effect). The effect of enzyme inhibition is typically rapid (e.g. often 1-2 days).
- See **Inducers, Inhibitors, & Substrates** pg 219 for examples of interactions, and see **Alternatives with Fewer Interactions** for some management suggestions.
- In general, if starting a new med (e.g. antihypertensives, anti-diabetics, pain meds) and concerned about inhibition from an existing med (e.g. fluvoxamine, amiodarone, diltiazem), start the new med at a lower initial dose and titrate up until response is seen.

Θ=inhibitor **ACEI**=angiotensin-converting enzyme inhibitor **AChEI**=acetylcholinesterase inhibitor **AE**=adverse effect **Al^{+++}**=aluminum **ARB**=angiotensinogen receptor blocker **ASA**=acetylsalicylic acid **BP**=blood pressure **BPH**=benign prostatic hyperplasia **Ca^{++}**=calcium **CCB**=calcium channel blocker **CV**=cardiovascular **CYP**=cytochrome P450 **DOAC**=direct oral anticoagulant **DI**=drug interaction **ECG**=electrocardiogram **Fe^{++}**=iron **GI**=gastrointestinal **HCV**=hepatitis C virus **HIV**=human immunodeficiency virus **INSTI**=integrase strand transfer inhibitor **K^{+}**=potassium **MAOI**=monoamine oxidase inhibitor **Mg^{++}**=magnesium **Na^{+}**=sodium **NSAID**=non-steroidal anti-inflammatory drug **PDE5I**=phosphodiesterase type-5 inhibitor **p-gp**=p-glycoprotein **PK**=pharmacokinetic **PPI**=proton pump inhibitor **S&Sx**=signs and symptoms **SS**=serotonin syndrome **SSRI**=selective serotonin reuptake inhibitor **TCA**=tricyclic antidepressant **WBC**=white blood cell

Clinical Concern			Mechanism / Management / Comments
Interactions with potential for AE or toxicity			
QT-Prolongation: see also RxFiles QT Prolongation e.g. sotalol, digoxin, citalopram, many others			• **Concern**: Torsades des pointes may occur due to additive QT-prolongation from medications. Also consider other (non-drug) risk factors for ↑QT. • **Management**: In general, patients with multiple risk factors should have a baseline ECG. Caution if QTc ≥ 450 msec; avoid QT-prolongers if QTc ≥ 500 msec or > 60 msec over baseline. See RxFiles QT Prolongation on page 10.
Serotonin Syndrome e.g. SSRIs, triptans, ergots, MAOIs, TCAs, lithium, methadone, tramadol, venlafaxine, duloxetine, vortioxetine, lasmiditan			• **Concern**: Serotonin syndrome is caused by excess serotonin. **s&sx**: agitation, excitement, delirium, ↑HR, hypomania, myoclonus, tremor, hyperreflexia, ataxia, weakness, fever/chills, diarrhea. Usual onset is within hours of medication change. • **Management**: Promptly discontinue new med if serotonin syndrome occurs & manage symptoms. Combo therapy with MAOIs + another serotonergic drug (esp. SSRIs) is contraindicated (high risk). Use a washout period or cross-taper when switching antidepressants (esp. MAOIs). See Antidepressants pg 177.
Anticholinergic AE (confusion, falls, etc.) e.g. antihistamines, TCAs, antimuscarinics, muscle relaxants			• **Concern**: Especially in older adults, anticholinergics can have additive AE and ↓ cognition. See RxFiles Anticholinergics page 152. • **Management**: Beers Criteria recommends avoiding strong anticholinergics & avoiding combinations of 3 or more CNS-active drugs in older adults (moderate quality evidence, strong recommendation).[31] Examples of strong anticholinergics include: antihistamines; benztropine; cyclobenzaprine; TCAs; paroxetine; some antipsychotics (chlorpromazine, clozapine, quetiapine, etc.); disopyramide; antimuscarinics; antispasmodics; prochlorperazine. See Geri-RxFiles 3rd edition.
Hyperkalemia e.g. ACEI, ARB, aliskiren, cotrimoxazole, trimethoprim, spironolactone, eplerenone, finerenone, amiloride, triamterene, potassium supplements, cyclosporine, tacrolimus, drospirenone, heparins			• **Concern**: Hyperkalemia can be serious/life-threatening & require hospitalization. Digoxin has ↓ efficacy in hyperkalemic pts. • **Management**: Monitor for muscle fatigue, weakness, paralysis, arrhythmias, nausea. Regularly monitor K^+ (e.g. q3months); ↑monitoring when starting a new agent (e.g. in 3-7 days for HF patients). Use extra caution if higher risk for electrolyte imbalances (e.g. renal disease, advanced age). Avoid combining ACEI + ARB. Consider whether K^+-losing diuretics (e.g. thiazide) or K^+-binder (e.g. polystyrene sodium) are indicated. Watch for dietary K^+ sources.
Hypoglycemia e.g. sulfonylureas, meglitinides, insulin, DPP4 inhibitors (sitagliptin, etc.), GLP1 agonists (semaglutide, etc.), SGLT2 inhibitors (empagliflozin, etc.), cotrimoxazole, quinine			• **Concern**: Risk of hypoglycemia is additive. ↑ risk of hypoglycemia & death when insulin combined with 3 oral diabetic agents to ↑ tx intensity.[ACCORD] Cotrimoxazole: has caused hospitalizations for hypoglycemia when prescribed with glyburide in older adults. • **Management**: Prevent hypoglycemia through patient education, blood glucose monitoring (especially when insulin prescribed or pt frail/functionally dependant; see RxFiles Hypoglycemia Perspectives), individualized glycemic targets (e.g. less aggressive where possible; see Glycemic Targets pg 47), flexible regimens (e.g. skip repaglinide dose if skipping a meal). Often rational to discontinue secretagogues when insulin is added. Keep fast-acting carbohydrate on hand (e.g. orange juice, glucose tablets). Increase monitoring when new agent added.
Increased Bleed Risk e.g. warfarin, DOACs, antiplatelets, NSAIDs, SSRIs, SNRIS, steroids, potassium supplements (GI bleeds), some herbals			• **Concern**: Agents increasing bleed risk are often prescribed together; regularly assess whether benefits outweigh harms. • **Management**: Limit combination duration where possible. Prescribe gastroprotection (e.g. a PPI) if high GI bleed risk (see RxFiles Acid Suppression pg 63). Consider the use of acetaminophen and opioids for pain management rather than NSAIDs. Refer to RxFiles DAPT & TT pages 17-18.
lithium	+	NSAIDs; diuretics; ACE/ARBs	• **Concern**: NSAIDs, diuretics, ACEIs, & ARBs can all ↑ lithium levels by decreasing kidney elimination. Thiazide diuretics may be the most predictable, usually increasing lithium levels by 25-40%. • **Management**: Monitor lithium levels (e.g. 3-5 days after starting interacting med) & for symptoms of lithium toxicity (e.g. nausea, tremor, drowsy, ataxia).
azathioprine or mercaptopurine	+	allopurinol or febuxostat	• **Concern**: Xanthine oxidase inhibitors (e.g. allopurinol, febuxostat) ↓↓metabolism of azathioprine & mercaptopurine. Toxic levels (& subsequent ↓WBC) can occur. • **Management**: If combination cannot be avoided, use only 25% of the usual thiopurine dose & carefully monitor WBCs (e.g. q1wk x 4wks, then q2wks x 4wks).
Interactions with potential for loss of efficacy			
fluoroquinolones; tetracyclines; levothyroxine; bisphosphonates; INSTIs (e.g. dolutegravir); others	+	Ca^{++}; Fe^{++}; Al^{+++}; Mg^{++} (including antacids, multivitamins)	• **Concern**: These minerals can bind to & ↓absorption of fluroquinolones, tetracyclines, levothyroxine, bisphosphonates, and INSTIs. • **Management**: As a general rule, wait >2hrs after interacting med before taking Ca^{++}, Fe^{++}, Al^{+++}, or Mg^{++}. Note that switching from antacid to PPI will not always address the interaction (e.g. most bisphosphonates ↓ absorption if low stomach acid).
AChEIs e.g. donepezil, galantamine, rivastigmine	+	**Anticholinergics** e.g. TCAs, antihistamines, antimuscarinics	• **Concern**: This combination results in competing cholinergic/anticholinergic actions. • **Management**: It is necessary to **prioritize** between cholinergic and anticholinergic activity (i.e. don't use oxybutynin to treat urinary incontinence caused by donepezil). See RxFiles Anticholinergics on page 152 for medications with anticholinergic activity. May also consider using memantine instead of an AChEI.
Dopamine Agonists e.g. levodopa, pramipexole	+	**Dopamine Antagonists** e.g. antipsychs, metoclopramide	• **Concern**: Competing actions results in ↓ therapeutic effect. • **Management**: Avoid combination in patients with Parkinson's. Clozapine and quetiapine appear to have the lowest interaction risk among antipsychotics; domperidone has much less interaction risk than metoclopramide (↓ blood-brain barrier penetration).
low-dose ASA	+	NSAIDs	• **Concern**: NSAIDs may interfere with the antiplatelet ability of ASA due to competition for platelet cyclooxygenase. • **Management**: Consider acetaminophen instead of an NSAID. Occasional, single doses of NSAIDs (esp. ibuprofen) given at least 2 hours after ASA appear not to cause an interaction. Celecoxib appears to not interact, but has its own separate ↑ CV risk.
rifampin	+	oral contraceptives	• **Concern**: Rifampin decreases oral contraceptive efficacy through CYP induction. • **Management**: Using a 2nd form of contraception (during treatment, and for 7 days after) is strongly recommended. Use ↑estrogen dose if chronic rifampin. • **Note**: Birth control failure while on some antibiotics (amoxicillin, ampicillin, metronidazole, tetracyclines) has been documented in case reports but data is limited; patients may wish to err on the side of caution and use a back-up method of birth control for the rest of the cycle.[70]

Patient Genetic Variability: CYP variability occurs for all enzymes except CYP3A4. Strictly speaking, this variability is not classified as a drug interaction. However, it has a similar effect – e.g. patients who have a poor ability to metabolize a drug may see increased adverse effects. **Genotype variability is usually unpredictable →** when possible, start meds at a low dose and titrate to response. E.g. ~10% pts poor metabolizers of 2D6 = ↑ risk of AE with TCAs, metoprolol, carvedilol, tramadol, others; ↓effect of codeine due to ↓bioactivation (& also ↑AE). E.g. ~4% pts ultrarapid metabolizers of 2D6 = ↑ toxicity with codeine and recent case report of breastfed infant death.[32] E.g. 0.3-0.6% of patients have deficiency in the enzyme thiopurine methyltransferase (TPMT) = ↑ toxicity with azathioprine or mercaptopurine; some guidelines recommend prior TPMT testing before prescribing these meds.

Some Contraindicated Combinations: triptans combined with ergot derivatives; nitrates combined with PDE5Is;[80] MAOIs combined with other antidepressants.

Drug Interactions: Inducers, Inhibitors, and Substrates

A Haines BSP, T Smart BSP, A Crawley BSP Sept 2024

Our RxFiles charts contain abbreviated drug interactions; this table provides a bit more detail. **Substrates** are metabolized by the given enzyme. Enzymes that are **induced** metabolize their substrates faster. Enzymes that are **inhibited** metabolize their substrates slower. Example: fluvoxamine is a CYP2C19 inhibitor. When given with amitriptyline it will cause ↑levels (↓metabolism) of amitriptyline.

	1A2	2C9	2C19	3A4	2D6
CYP Inducers					
STRONG	**carbamazepine, primidone, phenobarbital, rifampin**	**CBZ, rifampin, phenobarb, phenytoin, primidone**	**carbamazepine, phenytoin, rifampin**	**apalutamide, carbamazepine, lumacaftor, phenobarbital, phenytoin, primidone, rifabutin, rifampin**	Not inducible.
MODERATE	ritonavir, smoking	dexamethasone, ritonavir, St. John's Wort	St. John's Wort	bosentan, efavirenz, etravirine, modafinil, St. John's Wort	
CYP Inhibitors					
STRONG	**ciprofloxacin**, **fluvoxamine**	delavirdine, **gemfibrozil**	delavirdine, **fluconazole**, **fluvoxamine**, **gemfibrozil**, ticlopidine	atazanavir, boceprevir, **clarithromycin**, cobicistat, indinavir, **itraconazole**, ketoconazole, mifepristone, nefazodone, nelfinavir, paritaprevir, **posaconazole**, **ritonavir** (part of PAXLOVID), saquinavir, telaprevir, **voriconazole**	**bupropion**, cinacalcet, delavirdine, **fluoxetine**, **paroxetine**, **quinidine**, **ritonavir**, **terbinafine**, tipranavir
WEAK TO MODERATE	acyclovir, amiodarone, cimetidine, fluconazole, gemfibrozil, norfloxacin, ofloxacin, verapamil	amiodarone, cotrimoxazole, efavirenz, etravirine, fluconazole, fluoxetine, fluvastatin, fluvoxamine, isoniazid, ketoconazole, metronidazole, omeprazole, paroxetine, ticagrelor, quinine, valproate, voriconazole	cannabidiol, cimetidine, cinacalcet, efavirenz, eslicarbazepine, esomeprazole, etravirine, fluoxetine, isoniazid, ketoconazole, moclobemide, modafinil, omeprazole*, oxcarbazepine, voriconazole	amiodarone, aprepitant, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, grapefruit, imatinib, verapamil	amiodarone, chloroquine, cimetidine, clomipramine, cobicistat, diphenhydramine, dronedarone, duloxetine, fluvoxamine, haloperidol, isoniazid, ketoconazole, methadone, mirabegron, quinine, ticlopidine
CYP Substrates **Levels** ↑ by inhibitors & levels ↓ by inducers.	acetaminophen, amitriptyline, caffeine, clomipramine, **clopidogrel**, **clozapine**, cyclobenzaprine, desipramine, diazepam, diphenhydramine, duloxetine, erlotinib, estradiol, flutamide, fluvoxamine, haloperidol, imipramine, **methadone**, olanzapine, ondansetron, pomalidomide, propranolol, tizanidine, **theophylline**, verapamil, **warfarin**	abrocitinib , amitriptyline, carvedilol, celecoxib, clomipramine, diazepam, diclofenac, diphenhydramine, doxepin, erdafitinib, fluoxetine, glimepiride, glyburide, ibuprofen, imipramine, indomethacin, irbesartan, lesinurad, losartan, **methadone**, montelukast, naproxen, omeprazole, **phenobarbital**, phenytoin, rosiglitazone, sildenafil, sulfamethoxazole, tamoxifen, valsartan, vardenafil, **warfarin**	abrocitinib, amitriptyline, citalopram, clobazam, clomipramine, clopidogrel, desipramine, diazepam, diphenhydramine, doxepin, escitalopram, indomethacin, mavacamten, **methadone**, **phenobarbital**, **phenytoin**, PPIs, progesterone, propranolol, sertraline, **warfarin**	abemaciclib, alfuzosin, alpelisib, alprazolam, amitriptyline, amiodarone, amlodipine, apalutamide, **apixaban**, aripiprazole, **atorvastatin**, avapritinib, brigatinib, budesonide, buprenorphine, cabozantinib , carbamazepine, chloroquine, citalopram, clarithro-/erythro-mycin, clonazepam, **colchicine**, copanlisib, cyclosporine, darolutamide, deflazacort, dexamethasone, diltiazem, domperidone, donepezil, drospirenone, efavirenz, elagolix, eletriptan, elexacaftor, entrectinib, erdafitinib, ergot derivatives, estradiol, fedratinib, felodipine, fentanyl, finerenone, fluticasone, galantamine, gilteritinib, glasdegib, haloperidol, hydrocodone, istradefylline, ivabradine, ivacaftor, larotrectinib, lemborexant, lomitapide, lorlatinib, lumateperone, **lovastatin**, mavacamten, methadone, midazolam, nintedanib, neratinib, nevirapine, nifedipine, olaparib, oral contraceptives, oxycodone, paroxetine, pimavanserin, PKIs cancer, PPIs, praziquantel, quetiapine, ribociclib, rifabutin, risperidone, ritonavir, **rivaroxaban**, saxagliptin, sertraline, sildenafil, simvastatin, sunitinib, **tacrolimus**, tadalafil, tamoxifen, tamsulosin, tezacaftor, ticagrelor, tolterodine, tolvaptan, trazodone, triazolam, upadacitinib, ubrogepant, velpatasvir, venetoclax, verapamil, vilazodone. **warfarin,** zopiclone. (Many **oncology** meds: including many -**nibs**)	amitriptyline, amphetamine, aripiprazole, atomoxetine, bisoprolol, carvedilol, chloroquine, clomipramine, clozapine, codeine, cyclobenzaprine, cyclophosphamide, desipramine, dextromethorphan, diphenhydramine, donepezil, doxepin, duloxetine, eliglustat, fesoterodine, flecainide, fluoxetine, fluvoxamine, galantamine, gefitinib, haloperidol, hydrocodone, imipramine, methamphetamine, metoprolol, mirtazapine, nortriptyline, olanzapine, ondansetron, oxycodone, paroxetine, perphenazine, propranolol, risperidone, **ritonavir**, tamoxifen, timolol, tramadol, trazodone, venlafaxine, zuclopenthixol

***Omeprazole & Clopidogrel**: omeprazole (and esomeprazole) may ↓ clopidogrel's conversion to active drug. Some evidence suggests not clinically significant. May consider changing PPI to pantoprazole, lansoprazole, or rabeprazole.

P-glycoprotein (p-gp) is an efflux pump; it removes drug from a cell. The results of inhibiting or inducing p-gp depend on its location in the body. However, in the majority of cases inhibiting p-glycoprotein increases drug levels, as the pump is highly prevalent along the intestinal tract (& inhibition here prevents drug from being put back into the gut). For example, dabigatran (p-gp substrate) will have increased levels when given with verapamil (p-gp inhibitor).

P-Gp Inducers	carbamazepine, dexamethasone, phenobarbital, phenytoin, primidone, rifampin, St. John's Wort
P-Gp Inhibitors	amiodarone, **carvedilol**, clarithromycin, cobicistat, **cyclosporine**, **daclatasvir**, diltiazem, dronedarone, duloxetine, erythromycin, grapefruit, indinavir, itraconazole, ketoconazole, ledipasvir, **mefloquine**, mifepristone, nelfinavir, paritaprevir, posaconazole, **propafenone**, quinidine, ritonavir, saquinavir, **simeprevir**, tacrolimus, **tamoxifen**, telaprevir, ticagrelor, velpatasvir, verapamil
P-Gp Substrates	amiodarone, **apixaban**, boceprevir, citalopram, cyclosporine, **dabigatran**, dexamethasone, **digoxin**, diltiazem, **edoxaban**, erythromycin, gilteritinib, indinavir, loperamide, lovastatin, nelfinavir, posaconazole, prednisone, ranitidine, rifampin, ritonavir, **rivaroxaban**, saquinavir, sertraline, sofosbuvir, talazoparib, telaprevir, velpatasvir, verapamil. (**Oncology** meds: including many -nibs)

Organic anion-transporting polypeptides (OATPs) are influx pumps; they pumps drug into a cell. The results of inhibiting OATP depend on its location: if at the kidney, ↑levels; if at the liver, ↑levels; if in the GI tract, ↓levels. For example, simvastatin (OATP substrate in the liver) will have increased levels when given with cyclosporine (OATP inhibitor).

OATP Inhibitors	clarithromycin, cobicistat, cyclosporine, erythromycin, gemfibrozil, grapefruit, ketoconazole, rifampin, ritonavir, saquinavir, telaprevir, velpatasvir, & voxilaprevir
OATP Substrates	ARBs, ciprofloxacin, erythromycin, montelukast, revefenacin, statins

HERBALS: Drug Interaction Chart [1,2,3,4,8,10,11,12]

B Jensen BSP, A Crawley BSP July 2023

Clinical Pearls

- Natural medicine does **NOT** guarantee **SAFETY**. Medicinal herbs are drugs with potential harm & benefit; like all drugs, serious AE & DI's can occur.
- Many herbals interact with warfarin (marked with ⓦ on chart & see right column)
- Herbals with well-documented DI's include: **St. John's Wort** (induces p-gp & CYP3A4), ginkgo, ginseng, & ephedra. For many herbal products, interactions are not well-studied. Useful herbal DI resource: www.ncbi.nlm.nih.gov/pmc/articles/PMC4813519.
- Herbal products highlighted in red are generally regarded as unsafe; **avoid use**.
- Guidelines often recommend stopping **all** herbals 1 week prior to surgery since purity, evidence uncertain; herbals marked Ⓟ are of particular concern when given pre-op.[JAMA 2001]
- Doses highlighted in white have some evidence for efficacy, but watch for DI & AE.
- High risk of drug interactions in **cancer or transplant** treated patients.
- Those who use complementary medicine are more likely to refuse chemotherapy tx.

Some Herbal Products with Potential Warfarin Interactions ⓦ

↑INR: agrimony, angelica, anise, arnica (wolf bane), asafoetida, black cohosh, bogbean, borage seed oil, bromelain, capsicum, cassia, celery, chamomile, chondroitin, clove, cranberry, danshen, DHEA, devil's claw (may ↑purpura risk), dong quai, echinacea, evening primrose oil, fenugreek, feverfew, flaxseed, garlic, ginger, ginkgo, ginseng, glucosamine, horse chesnut, horseradish, kratum, licorice, lovage root, meadowsweet, melilot (sweet clover), milk thistle, noscapine, onion, papain (papaya), parsley, passionflower, poplar, prickly ash, quassia, red clover, royal jelly, rue, saw palmetto, sweet clover, tonka bean, tumeric, umbelliferae, Vitamin E, woodruff, & willow (wintergreen)

↓INR: agrimony, Co-Enzyme Q10, dandelion, green tea, mistletoe, nettle, parsley, plantain (black psyllium), psyllium, St. John's Wort, yarrow

Useful Resources, Tools, and Links

see **Online Extras** 🖳 for more websites

Natural Medicines Comprehensive Database www.naturaldatabase.com; **Herbal Products & CKD** www.herbalckd.com;
National Institutes of Health nccih.nih.gov/health/herbsataglance.htm
Easy-to-read summaries, for both patients and practitioners, & App available: www.mskcc.org/aboutherbs
Health Canada www.hc-sc.gc.ca/dhp-mps/prodnatur/index-eng.php & **FDA** www.fda.gov/food/dietarysupplements/default.htm guides to herbal products

HERB/ Botanical name	DRUG INTERACTIONS DI / ADVERSE EVENTS AE / CONTRAINDICATIONS CI
AGRIMONY ⓦ	DI warfarin may ↑↓ INR AE photo dermatitis, ? ↓BG
ALFALFA/ ⓦ Medicago sativa	DI cholesterol meds → may further ↓ lipids; cyclosporine/steroids → ? immuno-stimulating; **hypoglycemics** → may further ↓ BG; warfarin ↑↓ INR→ may contain warf constituents or Vit K AE May ↑K^+, rare pancytopenia, worsening lupus, photosensitivity; Rare: salmonella; CI Lupus
ALOE/Aloe vera (not Aloe latex)	DI insulin; ?digoxin & thiazide ↑ cardiac AE due to electrolyte imbalance; glyburide → may further↓BG AE thyroid dysfunction Case report, contact dermatitis, ↓K^+ (especially with insulin), liver damage Case reports CI Breastfeeding
ANGELICA ⓦ	DI warfarin AE photo dermatitis CI Breastfeeding, Pregnancy: caution ↑ uterine contractions
ANISE/ Aniseed ⓦ	DI MAOIs → may ↑ risk of HTN crisis; warfarin ↑ INR → may contain warfarin constituents
ARISTOLOCHIA in Xie Gan Wan	DI AMIO, STanabolic, KTZ, MTX → additive **hepatotoxicity** AE **nephrotoxicity, cancer**.[HCND warning '05, Chen'12]
AYURVEDIC syrup	DI phenytoin→ ↓ [phenytoin] & efficacy AE heavy metal poisoning - 20% have lead/mercury/arsenic [Saper04&08]
BETEL NUT/Areca catechu	DI antipsychotics→ may↑**EPS (strong cholinergic AE)** AE red stain (mouth & feces), poor asthma control
BLACK COHOSH/ ⓦ Cimicifuga racemosa **REMIFEM 20mg BID**	DI hormones→ may have **estrogen**-like effect. Equivalent dose ~40-80mg/day; iron→ tannic acids may ↓ iron absorption; cisplatin?; warfarin ↑INR→ may contain **salicylates.** AE mild GI effects & ↓ **BP;** Rare ↑ **LFT**.[Health Canada '05] Used for menopausal symptoms, ?**Not** effective[Newton'06,Geller'09]
BLADDERWRACK/ ⓦ	DI warfarin↑INR; levothyroxine → herb is source of iodine → caused **hyperthyroidism.** AKA Fucus, Kelp
BOGBEAN ⓦ	DI warfarin ↑ INR → may have hemolytic activity
BORAGE ⓦ -oil **not** for eczema [Bamford'13]	DI antipsychotics/anticonvulsants/TCAs→ may ↑ **seizures**; AMIO, STanabolic, KTZ, methotrexate→ may ↑ **hepatotoxicity**. Not helpful for atopic dermatitis.[Takwale 2003]
BROOM	DI Antihypertensive meds → herb may ↑ BP
CALAMUS	DI Sedatives→ may potentiate sedation. Carcinogenic!
CAPSICUM/ Chili peppers	DI MAOIs→ ↑risk of HTN crisis; **ACE inhibitors** → may ↑ **cough**; **theophylline** → may ↑absorption AE dermatitis, GI upset.
CASCARA/ Rhamnus purshiana	DI Various meds→ ↓ absorption by ↓ GI transit time; digoxin/thiazides/steroids→ may potentiate **hypokalemia**
CELERY (seed/extract) ⓦ	DI warfarin ↑INR→ may contain warfarin constituents; sedatives→ potentiate sedation. AE diuretic
CEREUS	DI MAOIs/SSRIs/TCAs → may ↑ risk of serotonin syndrome
CHAMOMILE/ ⓦ Matricaria recutita (German/Roman)	DI warfarin ↑ INR → may contain warfarin constituents, ↑bleed [Segal'06]; iron → tannic acids may ↓ iron absorption; **sedatives**→ may ↑ sedation; AE allergic reactions, conjunctivitis. May help anxiety [Amsterdam '09]
CHAPARRAL Larrea tridentata	DI AMIO, STanabolic, KTZ, MTX → may have additive **hepatotoxicity**.[Health Canada '05]
CHINESE HERB MIXTURE	AE Rare: heavy metal **contamination**. Not helpful for Hepatits C [Jakkula 04]
CHONDROITIN ⓦ **1200mg/ day** [Reichenbach'07] IM in other countries	DI warfarin ↑ **INR** → may ↑ bleed (chondroitin sulfate is part of antithrombotic-danaparoid) AE GI:↓ absorption ~10%, ?prostate cancer, ?bovine cartilage & bovine spongiform encephalitis risk. Minimal effect [Kahan, Michel'05,Wildi'11], but **800mg**/day [Concept] was similar to celecoxib 200mg/day in knee OA.
CHROMIUM picolinate♣po May ↓insulin resistance [FDA]	DI nephrotoxic drugs → may ↑ renal failure & rhabdomyolysis; levothyroxine; hypoglycemics → may ↓ BG [Nahas'09], not ↓ A1C [Kleefstra 06]. Not helpful for impaired glucose tolerance [Gunton'05]
COLTSFOOT/ Tussilago farfara	DI AMIO, STanabolic, KTZ, MTX → may have additive **hepatotoxic** effect. CI Breastfeeding.
COMFREY/ Symphytum sp	DI AMIO, STanabolic, KTZ, MTX → may have additive or innate **hepatotoxic** effect [Health Canada warning Dec '03].
CO-ENZYME Q10/ ⓦ Ubiquinone [PharmLet'10&Wyman'10,Bookstaver'12 =No]	DI beta blockers, phenothiazines, TCAs, doxorubicin → may ↓ cardiac AE from these meds. {60-200mg daily} limited studies in HF; cardiac meds & antihypertensives → may ↑ effect of cardiac meds; HMG-CoA &↓ BG → may ↓ natural [Q_{10}] in vivo; warfarin. AE GI, rash. Antiplatelet. Watch LFTs.
COUCH GRASS	DI diuretics → may ↑ K^+ loss; lithium → may alter level; sedatives → may potentiate sedation
CRANBERRY ⓦ	DI ?warfarin ↑ INR; hypoglycemics → may ↑↓**BG**; ↑levels of midazolam.
DANDELION ⓦ	DI diuretics→ ↑ effect; lithium → may ↑ lithium toxicity; warfarin ↓ INR→↓ effect [K⁺ content]; ↑K^+
DANSHEN ⓦ	DI warfarin ↑**INR** → **clinical bleed** due to ? acetylsalvianolic acid; digoxin: ↑ cardiovascular AEs
DHEA/ ⓦ Dehydroepian-drosterone	DI warfarin ↑ INR → may have fibrinolytic potential; triazolam ↑ level due to DHEA. AE Watch LFTs. Banned by the NFL/Olympics.[Med Let05]
DEVIL'S CLAW/ ⓦ Harpagophytum procumbens	DI heart & BP meds → may ↑↓ BP; hypoglycemics → may ↑↓**BG**; **warfarin** → ? purpura; analgesics→may ↑analgesia [? help back pain Gagnier'07]. AE headache, ringing ears, ↓appetite, ↓taste, GI.
DONG QUAI/ ⓦ Angelica sinensis	DI heart meds → **quinidine** like activity; warfarin ↑ **INR** → ? contain warfarin constituent Case reports AE photosensitive; >24wks/high dose carcinogenic? CI Breastfeeding
ECHINACEA ⓦ Ⓟ Purple coneflower (E. purpurea, pallida & angustifolia North America) **No↓ in infection** kids[Taylor JAMA 2003]; or adult cold[Turner NEJM 05,Barrett AIntMed 10]	DI AMIO, STanabolic, KTZ, MTX → may have additive **hepatotoxicity** if used for > 8 weeks; ?**corticosteroids/cyclosporin** → avoid combination; glycemic control → may ↑ ↓ BG; ?warfarin ↑ INR→ by ↓ warfarin metabolism; ↑ midazolam metabolism AE rash, **allergic** reaction, somnolence, dizziness, headache, GI upset, hepatotoxicity Case report CI HIV, **TB, transplant, RA, MS, lupus → herb immunostimulant**,<12yr [MHRA]. Often used for 2 weeks for an acute infection
ELECAMPANE	DI sedatives→ may potentiate sedation
EPHEDRA/ Ma huang Herbal Ecstasy EPHEDrine/ Pseudoephedrine Ban in Olympics ?~1% ePHEDrine. Tea~15-30mg ePHEDrine/cup. Ⓟ	DI anticonvulsants → ↑**seizure**; urine → false +ve with amphetamine, **caffeine**, decongestants; stimulants → ↑ nervousness; **heart & BP** meds → may ↑ HR & BP; hypoglycemics → may ↑↓ BG; dexamethasone → may ↓ level AE In many weight loss or energy products (>**800 reports** of nervousness, insomnia, irritability, psychosis, headache, dizziness, seizures, stroke, premature ventricular contraction, hypertension, **MI & death** especially with caffeine). May ↑↓ thyroid hormones. Hepatitis Case reports CI Breastfeeding. **FDA ban** [Apr/04] max: 8mg/dose & 24mg/day for ≤1week.
EVENING PRIMROSE OIL Oenothera biennis **not** for eczema [Bamford'13] ⓦ	DI **anaesthetics/antipsychotics**/anticonvulsants → may ↑**seizures; antiplatelet/warfarin** → contains GLA may ↑ **bleeding** AE nausea, headache, ↓ BP & soft stool. ? For menopause/itch & an EFA omega-6 source.
FENUGREEK ⓦ	DI warfarin ↑INR → may contain warfarin constituents AE may ↓ glucose [Nahas'09]; ?hemolysis [if G6PD]
FEVERFEW/ ⓦ Tanacetum parthenium **Tanacet 125mg daily** -only **6 of 30 lots** had labeled content[13]	DI iron→ tannic acids may ↓ iron absorption; **NSAIDs/Steroids**→ may ↓ therapeutic **effect** of feverfew; warfarin ↑ INR→ herb in vitro ? inhibit binding of platelets AE gastric discomfort, oral **ulcers**, lip/tongue swelling & rebound headache on discontinuation CI Breastfeeding. Often used for migraines - ? benefit[Pittler 04] Recommend 0.2%, most products contain <0.1% parthenolide.
FLAXSEED 40g/day ⓦ	Has ALA fatty acid, fibre; may ↓LDL (but not TG) at 40g/day. DI warfarin ↑INR AE gas, bloating, allergy.
GARLIC/ Allium sativum **Active agents**: allicin & ajoene (↑doses required; short t½ (3hr) & acid labile→enteric coate better; ?lipid effect [Gardner'07, Sun/17] ⓦ Ⓟ	DI antihypertensives → may ↓ **BP**; aspirin/warfarin ↑↓**INR** → ?bleed risk → ajoene [from allicin breakdown] ?responsible for **reversible** inhibition of platelet aggregation→ Case reports; hypoglycemics → may ↓ BG; oral contraceptives may ↓ levels; **ritonavir, saquinavir, isoniazid** → may ↓ drug levels. AE burning sensation, nausea, heartburn, menorrhagia, diaphoresis, lightheadedness, **odor**iferous skin & breath, contact dermatitis. Historically used for HTN & ↑**cholesterol.**
GERMANDER Teucrium chamaedrys	DI AMIO, STanabolic, KTZ, MTX → may have additive **hepatotoxic** effect; **30 cases of liver failure.**
GINGER/ Zingiber officinale ~250mg po TID White AFP'07 ⓦ	DI ? heart & antihypertensives → may ↑ or ↓ effect with these meds; ? hypoglycemics → may cause hypoglycemia; warfarin ↑ INR → may inhibit platelet aggregation (in vitro); ↑ crizotinib level. AE heartburn & allergic reactions. An antiemetic [Portnoi'03,Smith'04]
GINKGO BILOBA/ ⓦ Maidenhair Tree -? dementia Birks 2009, **no benefit** [Vellas '12: Guid Age] **~40mg po TID ac** (**not** helpful for mountain sickness) -possible CVD harm [GEM] Ⓟ	DI acetaminophen & ergotamine/caffeine →subarachnoid **hemorrhage** & subdural hematoma; bupropion/theophylline/anticonvulsant/TCA/trazodone → may ↑ seizure by ↓ threshold; **aspirin/clopidogrel/dipyridamole/ticlopidine/warfarin** ?↑**INR**→ ginkolide B may (-) platelet activating factor by displacement from receptor site Case reports; thiazides → combo may ↑ BP_1 case; omeprazole/insulin may ↓ levels; efavirnez/ritonavir ↓ levels; NSAIDs → may↑bleeding Case reports AE ? ↑ **strokes** in GEM trial, headache, dizziness, restlessness, N/V/D & dermal sensitivity. Used to help circulation & cognition. Reported antihypertensive effects & cardiac arrhythmias.

GINSENG/ Eleuthero or Siberian Eleutherococcus senticosus Ⓦ	DI heart & BP meds→ may change **BP**/↑HR; digoxin → **may ↑ digoxin** serum level; sedatives ↑ sedation; warfarin ↑INR → ?↓ platelet aggregation & contain coumarin. ?↑ LFTs with atorvastatin. AE May ↑K^+, ? assay interference with level or from contaminated P. sepium CI Breastfeeding
GINSENG, AMERICAN Panax quinquefolius Ⓦ **COLD-FX** promising Predy'05 Ⓟ **KOREAN/ASIAN** Panax ginseng -lacks evidence for cognition Geng'10, heart benefit Buettner05 & insulin sensitivity Reeds11; ginseng product survey1990: **~25%** contain ginseng & **85%** do NOT	DI alcohol → may ↑alcohol clearance; antibiotics → may ↑ effect; cholesterol meds→ may further ↓ lipids; ? corticosteroids → may affect [steroid]; ? heart & BP meds → **-ve chronotropic** & inotropic activity & may ↓ **BP;** cardiac meds → may ↑QTc interval; **estrogens/corticosteroids**→ ?additive effects reported mastalgia & postmenopausal bleeding; **furosemide** → case report of ↓ furosemide effect; hypoglycemics → **may further ↓ BG**; MAOIs → may inhibit reuptake of various NTs & ↑ tremor/**mania**; mood stabilizers → may **induce mania**; ?oral contraceptives → may ↓ sex hormone tx efficacy; ? **sedatives** → may potentiate/antagonize sedative AE; ? warfarin ↑↓ INR → may ↑ bleeding by itself or ↓ **INR** due↑warfarin metabolism (Case reports Yuan 2004) AE for ALL species: **nervousness**, excitation, diarrhea, insomnia, inability to concentrate, headache, hypertension, epistaxis, allergies, skin eruptions. CI Breastfeeding, MAOIs
GLUCOSAMINE sulf / HCL **~500mg po TID** Ⓦ LAKOTA has this & 8 other herbs ~90% absorbed; IV other countries	DI Hypoglycemics/insulin → does not ↑HgA1c Scroggie 2003, may ↑ insulin resistance; ? ↑ resistance to doxorubicin & etoposide; ?warfarin ↑INR. AE GI: e.g. diarrhea, ? shellfish allergy, ? ↑ IOP eye. Some efficacy Richy & Towheed. **Sulfate salt** better evidence. Used for osteoarthritis. Not recommended for symptomatic osteoarthritis of the knee AAOS 2013.
GOLDENSEAL/ Hydrastis canadensis	DI heart & antihypertensives→ can alter heart & BP; heparin→ can oppose the action of heparin; sedatives→ may ↑ sedation. May inhibit cytocrome **2D6** & **3A4**. **Expensive & often adulterated.**
GOTU KOLA	DI sedatives → may ↑ sedation; statins → may ↑ lipids
GREEN TEA Ⓦ	DI iron→ ↓absorption tannic acid; **warf ↓INR**→has ↑K^+ in vitro; **lithium** ↑ if stop caffeine; nadolol ↓level stimulants: 10-80mg caffeine/cup of tea AE ?↓BG Nahas'09, ?TTP Liatsos'10, ↓HTN Yang04, ↑LFTs Bonkovsky'06;Health CDN
GUAR GUM/ Cyamopsis tetragonolobus	DI digoxin & pen V → ↓ GI absorption; estrogen → ↓ absorption; glyburide, iron & **metformin**→ ↓absorption some formulations AE rare gastric obstruction, ? ↓ cholesterol levels. Fibre.
HAWTHORN/ Dahmer AFP'10 Crataegus monogyna	DI **digoxin &↓BP meds** → ↑ inotropic and vasodilatory effects Pittler'08 but not for HF SPICE trial; **Antiplatelets**: herb ↓THX A2,↑bleed; MAOIs: may contain tyramine→↑risk of HTN crisis. AE ↑K^+
HOPS	DI **sedatives**→ may ↑ sedation; estrogen → herb has estrogen like chemicals
HORSE CHESTNUT Ⓦ	DI warfarin, ?aspirin AE stomach irritant, ↓BG, ?↓venous insufficiency. Pittler06 AKA Aesculus hippocastanum
INDIAN snakeroot	DI antihypertensives & digoxin→ ↑effect; antidepressants → can↓ effect (reserpine in herb)
JAMAICAN Dogwood	DI sedatives → may potentiate sedative AE
KARELA/Bitter melon	DI hypoglycemics → may affect blood glucose levels Nahas'09
KAVA KAVA/ Piper methysticum Ⓟ **Stop-sale** order in Canada Aug/02 but may still be avail. Mills 03 ***-often a social drink in South Pacific***	DI alcohol/antipsychotics/sedatives→ may **↑ sedation;** alprazolam/benzo's → additive depression case report of ↑lethargy/?coma with alprazolam; P450 3A4 enzyme inhibition; antiparkinsonian meds → may exacerbate Parkinson's case report; antidepressants → may ↑ effect AE headache, dizziness, GI discomfort & local numbess after oral ingestion, **dry scaly skin** & yellow discoloration**,** leukopenia, **thrombocytopenia**, photosensitivity & eye redness with long term use or ↑ dosages, **hepatotoxicity** FDA 2002,Tesche'10. CI Breastfeeding. Often used for anxiety.
KELP	DI levothyroxine→ source of iodine→caused **hyperthyroidism**
KOMBUCHA	DI AMIO, STanabolic, KTZ, MTX→ may have additive **hepatotoxicity**. Source of **anthrax** outbreak.
KRATOM Mitragyna speciosa Ⓦ	Opioid-like. AE nausea,sedation,constipation,?seizure. DI 1A2, 2C19, 2D6, 3A4 other CNS depressant,?warf. Overdose
KYUSHIN	DI digoxin → may interfere with dynamics/monitoring
LICORICE/ Glycyrrhiza glabra Ⓦ High dose is >50 grams/day Most licorice in the USA contains anise oil rather than licorice.	May be OK if <30g/day. DI antihypertensives/digoxin/loop diuretics/spironolactone/thiazides → may ↓ K^+ & **Na^+ & fluid retention**, can **↑BP** (i.e. Pseudoaldosteronism), **encephalopathy; corticosteroids→ may ↑ oral & topical steroid** effects & AEs; **digoxin** → may interfere with pharmacodynamics/monitoring; hypoglycemics → may ↓ glucose tolerance; oral contraceptive → may cause HTN, edema, ↓ K^+, seizure Case report; ? warfarin ↑ INR → may inhibit platelet activity. AE lethargy, headache & electrolyte imbalances. ??help liver. Dhiman'05 CI Breastfeeding, ?pregnancy.
LIFE ROOT/Senecio aureus	DI AMIO, STanabolic, KTZ, MTX→ may have additive **hepatotoxicity**.
MILK THISTLE/ Silybum marianum IV in Europe Ⓦ	DI 2C9; antihypertensives → may ↓ effect; **hypoglycemics** → may further ↓ BG; may ↓ indinavir AE Gastric pain, diarrhea, vomiting & allergic rx. Oral ~25% absorbed. Does not help HCV Fried'12. IV to "detoxify the liver"?? Rambaldi'05".
NETTLE Ⓦ	DI iron → tannic acids may ↑ iron absorption; sedatives → herb may potentiate sedation; BP meds: may ↓ BP; warfarin ↓ INR → may contain Vitamin K AE GI, rash, ↑K^+
PAPAIN/Papaya Ⓦ	DI warfarin may ↑ INR **(Carica papaya)** AE gastritis, **allergy to: DIGIFAB**
PARSLEY Ⓦ	DI antihypertensives → sympathomimetics → watch for ↑ BP; **MAOIs**→ ↑ risk of HTN crisis. warfarin ↓ INR → may contain Vitamin K. AE photo dermatitis
PASSIONFLOWER Ⓦ	DI MAOIs/SSRIs/TCAs → may ↑ risk of **serotonin syndrome; sedatives**→ ↑ sedation; warfarin
PENNYROYAL/ Mentha pulegium	DI AMIO, STanabolic, KTZ, MTX→ may have additive h**epatotoxicity** (? Treat → acetylcysteine)
PLANTAIN/ Black psyllium Ⓦ	Fibre. Take with ↑ fluid. DI carbamazepine/digoxin/iron/lithium/warfarin→ ↓ absorption by herb; digoxin → may interfere with absorption/dynamics/monitoring. AE ↓BG
PLEURISY ROOT	DI digoxin additive effect; MAOIs → ↑ risk of hypertensive crisis
PSYLLIUM/ P.ovata Ⓦ	DI carbamazepine/digoxin/iron/lithium/warfarin → ↓ absorption. Fibre.
RED CLOVER promensil Ⓦ	DI contraceptives/tamoxifen/letrozole: may ↓ effect; warfarin. AE rash. Made cheetahs sterile.
ROYAL JELLY ↑$ vs B vit Ⓦ	DI asthma meds→may cause bronchospasm; warfarin. Severe allergies with bee products.
SAGE	DI anticonvulsants → ↑seizures; sedatives → herb may ↑sedation
SAIBOKU-TO Asian herb mix	DI corticosteroids→ ↑prednisolone levels. Same as→sho-saiko-to,Poria cocos,Mangolia officinalis&Perillae frutescens
SASSAFRAS	AKA S. albidum. AE sedation. Generally considered unsafe.
SAUROPUS androgynus	DI AMIO, STanabolic, KTZ, MTX → herb may potentiate **hepatotoxicity**
SAW PALMETTO/ Serenoa repens, Sabal fruit Ⓦ	DI ? **estrogen/contraceptive/hormone** → may have anti-androgen & estrogenic activity {160mg BID}? cause of floppy iris Syndrome; iron → tannic acids may ↓ iron absorption; ASA, warfarin: ? ↑ **bleeding** AE **headache**, GI (nausea, abd pain, constipation, diarrhea), may **↑BP**, rare hormonal actions (breast tenderness, loss of libido, venous thrombosis), pancreatitis, hepatotoxicity Case reports. Used for BPH. **No efficacy** Barry'11; Maybe?: ≤ PROSCAR but likely < than alpha 1 blockers.
SCULLCAP	DI AMIO,STanabolic,KTZ,MTX→may add to **hepatotoxicity**? due to adulterants; **sedatives**→may ↑sedation
SENNA/Cassia senna	DI digoxin/thiazides/steroids→may potentiate ↓ K^+; various meds→↓absorption →↓ time in GI
SHANKHPUSHPI	DI phenytoin→ **may ↓ phenytoin levels** as well as ↓ efficacy **(Ayurvedic mixed herb syrup)**
SHEPHERDS PURSE	DI MAOIs → may contain tyramine & ↑ risk of HTN crisis; sedatives→ may potentiate sedation
SHO-SAIKO-TO	DI prednisolone → ↓ levels for prednisolone **(Asian herb mixture)**
ST. JOHN'S WORT/ Hypericum perforatum **~300mg po TID** Ⓦ Ⓟ -**not for major depression** JAMA 01/& 02 but ?positive → Szegedi05, Linde08 & Gastpar06 for **Mild-Moderate** depression. **Active agents: 0.3% hypericin & hyperforin** (Used commonly especially in Germany) Hold for 2 weeks before any surgery**.** **Only 2/54 products contained within 10% of the labeled amount**. CJC Pharmacol 2003	DI Antihypertensive meds → may ↑ BP; barbiturates → may ↓ barbiturate induced sleeping time; **↓ levels** P-gp,3A4 of **alprazolam/amio-,drone-darone/antipsychotics/canagliflozin/ cyclosporine/dabigatran/alec, dasa, erlo, gefi, ibru, ima, lapa, nilo & suni-tinib / dig /exemestane / fexofenadine/ gliclazide/indinavir/ irinotecan / ivabradine / lamivudine / maraviroc/ midazolam/ naloxegol/ nevirapine/ omeprazole /oral contraceptive/ oxycodone/ regorafenib/ rilpivirine/ rivaroxaban/ simeprevir/ sirolimus/ sofosbuvir/ sorafenib /statin / sumatriptan / TCAs / theophylline/ tofacitinib/ venetoclax / verapamil /voriconazole/warfarin**→ P450 3A4 inducer; clopidogrel → may ↑ bleeding more active metabolite formed; iron → tannic acids can ↓ iron absorption; **MAOIs/SSRIs/TCAs**→ may ↑ risk of **serotonin syndrome** 6 case reports-tremor, delirium by so tyramine food restriction is wise because MAOI action; **narcotics** → may ↑ sleeping time; loperamide: delirium & agitation report; piroxicam/tetracyclines → can ↑ photosensitize rx; sedatives → may potentiate **sedation; thyroid** meds: may ↑ TSH; metformin → improved glucose tolerance via enhance insulin secretion. AE allergic reactions, headache, dizziness, restless, fatigue, dry mouth, mania, N/V, constipation, dreams, hair loss & **photosensitivity & possible uterotonic activity/**↓sperm**,** possible **cataract link**-rec to wear wrap around sunglasses. Often used for mild to moderate depression.
TAMARIND	DI aspirin → ↑ bioavailability of aspirin. AKA tamarindus indica.
TURMERIC curcumin Ⓦ	DI 3A4,1A2,2D6↓iron, ↑SSZ AE N/V/D. May help OA (1-2 g extract OD); not abd aortic aneurysm Garg'18; ? help fx dyspepsia 20
UZARA ROOT	DI **digoxin**→ may have additive effects or interfere with monitoring
VALERIAN/ Valeriana officinalis Ⓟ	DI ?sedatives, alprazolam → may potentiate sedation AE headache, excitability,ataxia & gastric complaints, ?acute **hepatitis** reported? Due to adulterants. Case report of withdrawal involving **cardiac abnormalities & delirium; & hyponatremia.** Used for sedative & anxiolytic action.
VERBENA/Vervain	DI MAOIs → ↑ risk of hypertensive crisis
WILD CARROT	DI sedatives → may potentiate sedation
WILD LETTUCE	DI sedatives → may potentiate sedation
WILLOW/Wintergreen Ⓦ	DI **warfarin ↑INR** → may contain **salicylate** constituent AE may affect BP
YOHIMBE/ Pausinystalia yohimbe	DI clonidine & antihypertensives → may ↑ BP∝ 2 blocker; **antidepressants TCA, MAOI** → may ↑ **HTN risk.** AE nervous, tremor,H/A, sz, arrhythmias, dizzy, flushing, ↑ urinary frequency & nausea, ↑HR/BP
XIAO CHAI HU TANG	DI corticosteroids → may ↓ **blood level of prednisolone**
XUEZHIKANG/ Red Yeast	DI caution with other hepatotoxic or antihyperlipidemic drugs

generally unsafe; consider white highlighted dose; Ⓦ=warfarin interaction; Ⓟ=a concern if given preoperative

ACE Inhibitor=angiotensin converting enzyme inhibitor **AE**=adverse effect **AMIO**=amiodarone **BP**=Blood pressure **BPH**=benign prostatic hyperplasia **BG**=blood glucose **CI**=Contraindication **CV**=cardiovascular **DI**=Drug Interaction **EPS**=extrapyramidal system **GI**=Gastrointestinal **HCND**=Health Canada **HF**=heart failure **HIV**=human immunodeficiency virus **HMG-CoA**=3-hydroxy-3-methyl-glutaryl-CoA reductase **HTN**=hypertension **IM**=intramuscular **INR**=international normalized ratio-ie. bleed risk **K^+**=potassium **KTZ**=ketoconazole **LFT**=liver function tests **MAOIs**=monoamine oxidase inhibitors **MHRN**=Medicines and Healthcare Products Regulatory Agency **MS**=multiple sclerosis **MTX**=methotrexate **RA**=rheumatoid arthritis **SSRIs**=selective serotonin reuptake inhibitors **STanabolic**=anabolic steroids **TB**=tuberculosis **TCAs**=tricyclic antidepressants **THX**=thromboxane **Vit K**=vitamin K **wks**=weeks **yr**=year

Concerns regarding purity, potency & quality are especially important in the herbal industry. Of a sample of 2609 sample of traditional Chinese medicines collected from 8 hospitals in Taiwan, 23.7% contained pharmaceutical adulterants e.g. acetaminophen, caffeine, hydrochlorothiazide, indomethacin & prednisolone.[5,7] Other NSAIDs & benzodiazepines have been found in Chinese patent medicines sold outside Asia.[6] In 24 of 251 Asian patent medicines there was lead; 36 arsenic & 35 contained mercury.[9] An analysis of 44 single product herbs from Canada & USA found only 48% had the stated ingredient, 59% had other ingredients such as feverfew, & 32% had a different herb in place of the labeled one.[14] 20% of hepatotoxicity in USA is due to herbal & dietary supplements esp. anabolic steroids.[15,16] 6 months after FDA recalls, 67% of supplements were still available for purchase, and remained adulterated.[17] Approximately 23,000 emergency department visits/yr in USA are attributed to adverse events related to herbal, complementary & micronutrient supplements.[18] Yet up to 85% of Canadians use natual health products.[19] Common cause of liver failure Devarbhavi'19

Notes: ¼ of all modern drugs have a natural/botanical origin e.g. red yeast may contain lovastatin. See **Online Extras** 💻: herbal products that frequently cause allergic reactions. ↑↑ adulterants eg. sildenafil, fluoxetine, steroids, silbutramine in supplements. Tucker'18