EVIDENCE-BASED MEDICINE (EBM) Overview: Notes on Validity, Precision & Contextualization of Results[1,2,3,4,5]

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For references/updates/extra info see: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-EBM-Overview.pdf

Critical Appraisal of Drug Studies [6,7]

A) Is the study valid?

1. Were patients randomized to treatment (tx) groups & was allocation concealed (AC)? {Without concealment, 37% bias in favor of tx. Sealed, opaque envelopes or central registry used to attain AC} [8,9]

B) Was everyone (patients, physicians, investigators, assessors) blinded to tx? {Especially important for assessors of subjective outcomes eg. Pain.}

1. Was the study controlled? (e.g. inclusion of placebo or active control group/arm; in an "N of 1" trial, patient is own control.)
2. Were treatment & control groups similar in prognostic factors for outcome of interest at beginning of study? If not, were adjustments made?
3. Were all patients accounted for at end? {Missing patients addressed?}
4. Was data analyzed based on groups patients were initially randomized to? {Intent to treat or ITT; protects integrity of prognostic randomization; per protocol (PP) analysis may also be of interest (e.g. non-inferiority trials}
5. Were patient groups treated similarly except for study intervention?
6. How was the study funded (role of funder)? Was study stopped early?
7. Was active comparator drug & dose a good choice?

C) What are the study results?

1. What was the primary (1°) endpoint? What were the secondary (2°) endpoints? Were endpoints & subgroups pre-specified?[10] Avoid data mining!
2. What was the difference between treatments? (Benefits & Harms)
3. Were the differences statistically significant? Clinically significant? {What were the 95% confidence intervals (CIs) or p values? Does the CI cross line of no effect?}
4. What are the absolute and relative risk reductions or increases?
5. What is the number needed to treat (NNT) or harm (NNH)?

D) Does this study matter to my patients?

1. How clinically relevant/important are the outcomes?
2. Were the patients similar to those in my practice? {Consider inclusion & exclusion criteria; very sick, old, young, drug interactions & complicated/co-morbid patients often excluded.}
3. Do treatment benefits outweigh the risks, costs & impact on life?

Types of Studies (from low to high level of evidence) [11]

- Case-control study: a retrospective observational study which selects patients with the outcome of interest (cases) & patients without that outcome (controls); attempts to find exposures linked to the outcome.
- Cohort study: an observational study in which two groups (cohorts) are observed over time for an outcome of interest. One cohort has exposure to a condition or treatment that the other does not. {Observational studies: association does not prove causation! Strength of association: RR: 1.01-1.5 *weak*; 1.51-3 *moderate*; >3 *strong*.[12]}
- Crossover study: a design in which each patient receives both treatments in two phases separated by a washout period. Each patient serves as own control, thus less variability in outcomes, & smaller sample size required; period effects may limit findings.
- Randomized controlled trial (RCT): a prospective study in which patients are randomized to treatment or control groups (equal chance at being assigned to any group). Groups are followed for outcome of interest.
- Systematic Review (SR): a systematic collection, review & presentation of available studies addressing a clinical question using specific criteria & methods; may include meta-analysis. e.g. *Cochrane*[13]/*Campbell*[14] *Reviews* {Meta-analysis: the combining of studies meeting prespecified criteria & addressing a clinical question. Results are calculated from the data of each study. Data is then pooled. ↑ sample size & statistical power useful if individual trials underpowered or subgroup analysis.}

[Level of evidence: SR > RCT > observational study > expert opinion.[15] Caution: Lots of low quality RCTs may not be better than 1 good quality RCT! A low quality SR, or a SR of low quality trials does not constitute high-level evidence.]

Terms: Related To Validity

- Bias: design flaws leading to over/underestimation of treatment effect e.g. recall bias, selection bias, publication bias; confounding factors esp observational studies
- Blinding: if investigators, patient etc are unaware of who receives tx vs control, they are less likely to inappropriately report better results with tx.

Study Results: Size Of The Treatment Effect [16,17,18,19]

- Event rate (ER): the number of people experiencing the event as a proportion of total number of people in the population or group
  - -Experimental ER (EER): {# events in experimental group / total in exp. group}
  - -Control group ER (CER): {# events in control group / total in control group}
- Relative risk (RR) or risk ratio: {EER/CER}
- Relative risk reduction (RRR): the RR subtracted from 1 {RRR=1–RR} [Whereas ARR varies with type of population treated, RRR is often more constant.]
- Absolute risk reduction (ARR): the arithmetic difference between the 2 event rates {CER – EER} [If ↑ risk: ARI= absolute risk increase]
- Number needed to treat (NNT): the number of patients who would have to be treated with the studied intervention for the studied time period for 1 of them to benefit. {NNT= 100 / ARR%}
- Number needed to harm (NNH): number of patients who would have to be treated with the studied intervention per studied time period for 1 extra person to experience the adverse event. {NNH = 100 / ARI%}
- Odds ratio (OR): = experimental event odds / control event odds; especially used in case-control studies where baseline risk is not known; also used in meta-analysis. When events are rare, the OR is similar to the RR; however, OR rate exaggerated relative to RR when events more common. {Link www.cebm.net: tool for converting OR to NNT[20]}
- Point estimate: the trial result used as best estimate of the true effect
- Hazard ratio (HR): like RR but more accurate; accounts for the time each participant was in the study before having event or withdrawing.

Study Results: Precision of Treatment Effect [21]

- Confidence Interval (CI): a 95% CI provides the range of values we are 95% certain that overlaps the true value. CI's indicates the precision of the estimate; where CI's are wide, they indicate less precise estimates of effect (just an estimate of the worst & best case scenario of the outcome) {For ratios, a CI that includes 1 means possibility of no difference. For ARR, ARI, NNT, NNH, a CI that includes zero means possibility of no difference between tx. Non-significant results eg. *trends* may provide clues for future research.}
- Type 1 (or α) error: *the false positive*; to find a difference when there is none. p-value: reflects type 1 error. A p <0.05 suggests a <1 in 20 probability that any difference is due to chance (statistically significant by convention). The smaller the p-value, the less likely that the result is due to chance.
- Type 2 (or β) error: *the false negative*; to conclude there is no difference when there really is a difference (e.g. if not enough patients enrolled)
- Heterogeneity: when studies within a meta-analysis have more variation than expected; may indicate inappropriate to combine studies.[22] {*Q statistic*: measure of within-study variance; I^2: ratio of variability among studies to total variation.}

Do the study results matter to me & my patients?

- Clinical significance vs statistical significance: some studies may detect extremely small statistically significant differences between groups; however magnitude of effect (e.g. NNT) may be too small to change practice. Evaluate both 1) the endpoint, & 2) the NNT or NNH. {e.g. small cognitive score improvement not noticeable to patient.[23,24]}
- Composite endpoints: combining endpoints can increase a study's power allowing for smaller or shorter trials. Outcomes should have similar value. Examination of individual outcomes can be important in interpretation as one endpoint may be the primary *driver*. {e.g. In DREAM, outcome of diabetes diagnosis the driver or death example of unequal endpoints.[25]}
- Surrogate endpoints: an endpoint meant to reflect / be correlated with another endpoint (eg. BP/LDL/A1c for CV events; CD4 cell count for HIV mortality). Clinical outcomes are more important since surrogate endpoints assume correlation with an outcome which may or may not always be true.[26] {eg. lower A1C target ≤6% ACCORD: but ↑ death, doxazosin ↓ BP ALLHAT but ↑ HF/stroke, & clofibrate WHO-CLOF ↓ LDL but ↑ death.}
- Other considerations: What uncertainties remain? Has drug been studied in enough patients to detect serious rare adverse events? What duration of intervention is studied & what are the potential benefits & risks over a longer term of exposure? Does real-world experience appear to be consistent with clinical trial data? Cost? How benefits & risks are described will also affect decisions.[27]
- What patient specific and societal values need to be considered?

Heads Up! Know what the numbers are telling you.

⇨ *You double your chance of winning a lottery if you buy a 2nd ticket; however your chance of winning is more related to whether 2 tickets or 2 million tickets are sold!*

- ***Beware of the Relatives*** ☺
  - Benefits are often given as relative numbers, whereas harms are often given as absolute numbers. This tends to exaggerate benefits & minimize the harms. ⇨Look for NNTs & NNHs.
    {e.g. Vioxx monograph 2004CPS: reported ~ 50% ↓ in GI complications with Vioxx 50mg/day vs naproxen 500mg BID & a thrombotic event rate of 1.8% (Vioxx) vs 0.6% (naproxen). Actual GI complications reductions 0.59% vs 1.37% (ARR=0.78; NNT=129); whereas thrombotic risk was worse (NNH=83).}
    {e.g. Oral contraceptives: risk of DVT in a younger, non-smoking ♀ may be ↑300% but absolute risk is <1.5/10,000 /yr & lower than risk in pregnancy}
- ***Non-Equivalent Durations & Risk/Benefit Perception***
  - Benefits are often given for total duration of trial which may be several years, whereas harms are often given per year.
    {e.g. UKPDS-33: aggressive glucose control benefit on microvascular endpoints given per 10 years; risks of hypoglycemia were given per year.[28]}
- ***Analysis: Pooling Together or Dividing Out***
  - Discussing the multiple benefits of a composite endpoint while individually sorting out risks may minimize risk perception.
    {e.g. In WHI, risk of just breast CA with HRT was 8/10,000 pt-years; yet risk of any harm (DVT, CHD, stroke, PE & breast cancer) was 1/66 over 5.2yrs.[29] }

Calculations Example: 1 yr trial	RRR	ARR	NNT	NNH
◆200 patients in Control group ◆200 patients in Treatment (Tx) group ◆Deaths: Control grp: 40. CER=40/200=0.2 Tx grp: 30. EER=30/200=0.15	= (0.20 - 0.15)/0.20 X 100 = 25% {risk of event is reduced by 25%}	20% - 15% = 5% {absolute risk of event is reduced by 5%}	= 100 / 5% = 20	if 60% of patients in Tx group experienced *headaches* compared with 27% in control group (ARI=33%) NNH= 100 / 33% = 3
For every 20 patients treated for 1yr, there is 1 less *death*; & for every 3 patients treated there will be 1 extra *headache*.				

A few NNTs / NNHs of interest	NNT
↓ mortality with simvastatin 20-40mg/day over 5.4yrs vs placebo in patients with CHD 4S	30 / 5.4yrs
↓ mortality with metformin 2550mg/day over 10 years vs non-intensive in obese T2DM patients UKPDS-34	14 / 10 yrs
↓ CV death/MI/stroke; clopidogrel 75mg/day + ASA vs ASA alone in ACS pts (↑ bleeding: NNH=99) CURE	48 / 9mo
↓ pain by ≥50% with TCAs (e.g. amiltriptyline 100mg/day) vs placebo in neuropathic pain (short term trials)	2

What makes for a good NNT? *It all depends!!!* NNTs will vary greatly with variations in baseline population risk, duration of tx, & type & number of endpoints included in composite. The value of the endpoint also varies from patient to patient.

ANTI-HYPERGLYCEMIC DIABETES AGENTS: Outcomes Comparison Summary Table Glucose Lowering in T2DM

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Drug Class		Sulfonylureas		TZDs			Meglitinides	DDP-4 Inhibitors	GLP-1 Agonists (Subcut)	SGLT-2 Inhibitors	Insulin in T2DM	
Generic ⇨ Brand	Metformin (MF) Glucophage, Glycon	Gliclazide Diamicron	Glyburide Diabeta	Pioglitazone Actos	Rosiglitazone Avandia	Acarbose Glucobay	Repaglinide Gluconorm / Nateglinide Starlix DC'D	Saxagliptin Onglyza, Sitagliptin Januvia, Alogliptin Nesina, Linagliptin Trajenta	Liraglutide Victoza, Exenatide Byetta, Dulaglutide Trulicity, Lixisenatide Lyxumia, Semaglutide, Albiglutide Eperzan	Canagliflozin Invokana, Dapagliflozin Forxiga / Farxiga, Empagliflozin Jardiance, Ertugliflozin	Intensity: Less (NPH HS + MF)	Intensity: More (Multiple daily doses)
		[Glipizide Glucotrol USA Spread-DIMCAD]										
Major trials to support findings/ Outcomes*	UKPDS-33,34,80 (ADOPT; some use in ADVANCE)	ADVANCE	UKPDS-33,80 (ADOPT)	ProACTIVE Ferwana M. Meta-analysis 2013. IRIS	Meta-analysis. RECORD interim, ADOPT, DREAM	(Prevention trial: Stop-NIDDM)	-	SAVOR-TIMI 53, TECOS, EXAMINE, CARMELINA (2018), PROLOGUE (2016)	ELIXA, LEADER, SUSTAIN6, EXSCEL (2018), REWIND (2018), HARMONY (2019)	EMPA-REG, CANVAS (2017), DECLARE (2019), VERTIS CV (2019)	T2DM UKPDS-33,80; ADVANCE, ACCORD, VADT, ORIGIN. Placebo group had ↑ insulin use in LEADER. (T1DM: DCCT/EDIC)(Also Boussageon et al Meta-analysis. BMJ 2011;343:d4169)	
↓ Risk of Death / Major CV[1]	✓✓✓[2] in obese, ↓ mortality NNT=14/10y, ↓ MI NNT=14/10y (UKPDS-34)	✓[3,4,5]	✓[4,5]	✓✓[7] ↓ MACE NNT=50/2.9y, but 1° composite endpoint not significant (ProACTIVE)	X?[8]	✓✓[9] in IFG, ↓ MACE NNT=40/3.3y	?	✓[10] saxagliptin, alogliptin, sitagliptin ↔ non-inferior to placebo for MACE, *But see ?HF below* ?[11] (linagliptin ongoing). Sitagliptin no effect on intima-media thickness PROLOGUE	✓✓✓[12] liraglutide ↓ MACE NNT=53/3.8 y (North American subgroup neutral), ↓ mortality NNT=72/3.8 y (LEADER), semaglutide superior to placebo NNT=44/2 y for MACE (SUSTAIN-6) ✓[13] lixisenatide ↔ non-inferior to placebo for MACE (ELIXA) ?[14] (exenatide, dulaglutide, albiglutide ongoing)	✓✓✓[15] empagliflozin ↓ MACE NNT=63/3.1 y, ↓ mortality NNT=39/3.1 y (EMPA-REG) ?[16] (dapagliflozin, ertugliflozin ongoing) ✓?[16] canagliflozin NS ↑ MACE in 1st 30days; NS ↓ MACE after 30days HR 0.89 (0.64-1.25) CANVAS interim data	✓[17,18]	✓[18,19,20] /X?[21] > insulin use with intensive target vs standard therapy, ↑ all-cause death NNH=95/3.5 y, & CV death NNH=125/3.5 y (ACCORD)
Effect on A1C**	✓✓✓	✓✓✓	✓✓✓	✓✓	✓✓	✓	✓✓ ✓	✓	✓✓	✓✓	✓✓	✓✓✓
Weight (loss vs neutral vs gain)	✓✓✓[A1]	X[A2]	X[A2]	XX[A3]	XX[A4]	✓✓[A5]	X[A6]	✓[A7]	✓✓✓[A8]	✓✓✓[A9]	✓[A10]	XX[A10]
↓ Risk of Hypoglycemia	✓✓✓	✓ ? If less risk with MR formulation	X Severe, occurs at 1.4%/yr	✓✓ Low risk with monotherapy	✓	✓✓✓	✓ ✓✓✓	✓✓?	✓✓?	✓✓ Risk when given with sulfonylurea or insulin	✓	XX Rate of 1.8%/yr
↓ Risk of HF / Edema	✓✓[22,23] 1st line in HF with eGFR >30 mL/min (CDA'13)	✓[23,24] (↑ CHF risk)	✓[23,25] (↑ CHF risk)	XX[26] ↑ HF NNH=50/2.9y, edema NNH=8/2.9 y	XX[25,27] ↑ HF NNH=69/5.5y, (RECORD), ↑ HF NNH=250/3y (DREAM)	✓[28]	✓[29]	X?[30] ↑ HF saxagliptin NNH=143/2.1 y (SAVOR), alogliptin (post hoc) (EXAMINE) sitagliptin HF neutral	✓[31] liraglutide (LEADER) and lixisenatide (ELIXA) neutral	✓[32] empagliflozin (EMPA-REG) neutral; (possible benefit: ↓hospitalizations)	✓[33,34] (↑ CHF risk)	✓[34] (↑ CHF risk)
Effect on GI tolerability	X Start low & titrate	✓✓	✓✓ rate of 1.8%/yr	✓✓	✓✓	XX	✓✓	✓✓	✓ Nausea, vomiting, diarrhea	✓ Nausea/diarrhea with dapagliflozin	✓✓✓	✓✓✓
Cost	✓✓✓	✓✓✓	✓✓✓	X	XX	✓✓	✓✓	X	XX	XX	✓	XX
Other	May have to hold or ↓ dose in acute illness/HF/ renal dysfx (? lactic acidosis); may ↓ B12. 1st line for obese T2DM (UKPDS-34)	Used in combination with metformin (ADVANCE)	Caution: ↓ renal function (& older adults)	X FDA +/- HC warnings:[35] ?↑ HF *(see above)*, ?↑ fractures ♀ (NNH~30/~3.5 y) ?↑ macular edema (conflicting data) **Pio**:?↑ bladder ca >12 mos (27.5 excess /100,000 person yrs), avoid co-admin with dapagliflozin[36] **Rosi**: Restricted access in CDN (SK-EDS) (↑ CV risk concerns)[37]		✓✓ PPG, Possible benefit of laxative effect in some TID dosing	✓✓ PPG, flexibility with meals TID dosing	✓ PPG FDA +/- HC warning:[38] HF (saxa & alogliptin); arthralgia, hypersensitivity rx, ?↑ pancreatitis,[39] pancreatic cancer[40] Linagliptin: no renal dose adjustment X new agents – outcome & safety data still limited	✓ PPG injection site irritation ?↑ pancreatitis,[39] pancreatic cancer,[40] ?↑ thyroid cancer (liraglutide)[41] (new *once weekly* agents may have ↓ GI adverse events)[42] ?gallbladder disease[46] X new agents – outcome & safety data still limited	X new agents – outcome & safety data still limited FDA +/- HC warning: ketoacidosis (DKA), AKI (caution: ↓ intravascular volume & ↓renal function Cana + Dapa), ↓BP; urosepsis/pyelonephritis, ↑fracture/↓BMD (canagliflozin), ↑ (~2x) limb amputations (canagliflozin),[43] ↑ UTI OR 1.34 & genital tract Infection OR 3.5 vs placebo, dapagliflozin ?↑bladder/ breast cancer (avoid with pioglitazone).[44,45]	✓ Fear/ perception of insulin injections	✓✓PPG Fear/ perception of insulin injections
Overall	✓✓✓	✓✓	✓	✓?	X?	✓	✓	✓?	? ✓✓ Liraglutide (CV/mortality benefit)	? ✓✓ Empaglifozin (CV/mortality benefit)	✓ ✓✓	✓✓ X?

*Drugs that lower blood glucose come with various levels of evidence regarding their balance of benefits & harms. This chart relies on current evidence, especially from randomized controlled trials that have evaluated patient oriented outcomes. Direct comparisons between agents have not been done so one is left to evaluate each drug for its relative advantages & disadvantages. **A1C will vary depending on dose, combinations & initial A1C.

See full version of this ANTI-HYPERGLYCEMIC DIABETES AGENTS: Outcomes Comparison Summary Table online for additional notes: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf

See also: ***RxFiles Diabetes Landmark Trials Summary*** *at:* http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf ***Diabetes Oral Agents Comparison Chart***: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-diabetes.pdf

Individualize approach considering balance of potential benefits & harms. Over-aggressive pursuit of targets can ↑mortality. ACCORD

An Advantage		Neutral	A Disadvantage
✓✓✓	✓✓	✓	X XX

ANTI-HYPERGLYCEMIC AGENTS (AHA): Comparison Chart [19,20,21,22,23,24,25,26,27 ADA 2017, 28,29,30 CDA 2013 & 2016 Interim, 31,32]

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Generic/TRADE/ Strength/Pregnancy	INITIAL & (Max) DOSE	USUAL DOSE RANGE	$ /100 day	KINETICS	EFFECTS ON: FBG	PPG	A1C↓%	LDL	HDL	TGs	Wt	DRUG INTERACTIONS (DI)	COMMENTS
Biguanides – ↓↓↓ hepatic glucose production; ↑ insulin sensitivity & cellular glucose uptake & utilization; ↓ morbidity & mortality NNT=14 /10yr (RRR ↓27%) **in obese patients (UKPDS-34). Take with food.**													
Metformin [33] **(MF)** PL **GLUCOPHAGE, GLYCON, g** 500ˢ, 850mg tab Metformin ER tab (ghost tab) **GLUMETZA** ✗ ⊗ 500mg, 1000mg tabs **once daily dosing {ghost tab shell may be passed in stool after releasing drug}	**250-500mg daily** (Max: **2550mg**/day, 850mg TID; but usual max 1g BID)	500mg po BID 850mg BID DPP 1g po BID ADOPT 1700mg am, 850mg pm	21 **24** **31** UKPDS 30	Onset – days to max effect at 2weeks Peak = 3h Duration = 8-12h	↓	↓	↓↓ 1-1.5	↓	↑	↓	-/↓↓ ↓2.9kg ADOPT 4yr	Metformin •**EtOH** & cimetidine, trimethoprim: ↑ effect of MF •contrast media (acute renal dysfn) •long-term ↓ $VitB_{12}$ & folate absorption •may ↓ TSH in treated hypothyroid pts	**1st line agent; DOC for OBESE !** Possible **wt loss**. Does **not** by itself cause **hypoglycemia. Elderly**: ↓dose.[34]; **Prevent** NIDDM[35 DPP]. Use in PCOS[36]. Low breast milk[conc.]; ↓open angle glaucoma. **AE: GI** (dyspepsia, N/D): **To avoid, start low dose & ↑ q2-4wk**; TID dosing option for larger doses to ↓GI intolerance Lactic acidosis <1:10,000[7 watch Na bicarb]. Anemia may occur long-term due to ↓Vit B12 absorption [7%] - consider oral B12 **Avoid**: ↓renal fx (<30 ml/min), acute/decompensated HF, liver dx Hold: in acute illness/dehydration, 48hr post [iodinated contrast esp. if CrCl<60] Combo MF/Rosi ↓A1C by ~2% but ↑edema & hypoglycemia vs MF alone. **Dialysis Dose:** 250mg/day in **peritoneal**; 500mg after each dialysis in **hemodialysis**
	Renal :↓ dose if CrCl **45-60**ml/min, 1000-1700mg/day; if **30-45**ml/min, 500-850mg/day. May avoid if **<30**ml/min.						**1-1.5**					**+'ve effect on lipids & wt!**	
	Metformin Combination Products see below and ⇒ Metformin/**Rosiglitazone** AVANDAMET ☎ ⊗ Metformin/**Sitagliptin** JANUMET ☎ ✆ (XR ☎ ✆) Metformin/**Saxagliptin** KOMBOGLYZE ☎ ✆ Metformin/**Linagliptin** JENTADUETO ☎ ⊗ (XR **FDA'16**) Metformin/**Dapagliflozin** XIGDUO ✗ ⊗				Metformin/**Canagliflozin** INVOKAMET 500, 850 & 1000mg///50 & 150mg tab BID cc ✗ ⊗$337 Metformin/**Empagliflozin** SYNJARDY 500, 850 & 1000mg///5 & 12.5mg tab BID cc ✗ ⊗ $316 **Combination Products, NOT in Canada:** Metformin/**Pioglitazone** ACTOplus met 500/15mg, 850/15mg BID; & ACTOplus met XR.							
Sulfonylureas (SU) – insulin secretagogue; ↑↑↑ β cell insulin release; ↑peripheral glucose utilization (↑ #/sensitivity of insulin receptors?); ↓hepatic gluconeogenesis; may stop if on insulin or ? DOC HNF1A/4A-MODY													
Chlorpropamide PL DIABINESE, g ⊗ 100, 250mgˢ tabs **D/C 2017**	100mg daily (500mg daily)	100mg po daily 250mg po daily	19 19	Peak = 6-8h Dur = 24-**72h**	chlorpropamide **not recommended** due to ↑BP & ↑ retinopathy (UKPDS-33)							↑ by 2C9 inhibitors eg. Amiodarone, SMX/TMP, fluvastatin…	In general, SUs achieve ~75% of effect at **1/2 their max dose**. Caution in elderly (hypoglycemia risk) & obese (wt gain). **Dose titration q1-2 weeks**. Failure rates ~5-10%/year. Reduce dose if **renal/hepatic** dysfx or if hypoglycemia. Many (~75%) require 2nd agent for BG control [eg. + MF or TZD]
Gliclazide DIAMICRON, g ✗ ▼ 80mgˢ tab **DIAMICRON MR, g** PL 30mg, 60mgˢ tab	40mg (160mg BID) 30mg MR (120mg daily [Advance])	80mg po BID 60mg MR po daily 120mg MR po daily	**29-72ˣ** [contract price varies] 30 57	Peak = 4-6h Dur =10-**24h**	Total Wt gain with glyburide >4kg vs **>6kg insulin** (UKPDS-33)[10yr]							• ↑ Hypoglycemia with: cimetidine, clarithromycin, **EtOH**, fluconazole, fluoxetine, MAOIs, metronidazole, NSAIDs, quinolones,salicylates & sulfonamides • β-Blockers may mask hypoglycemia • Disulfiram rxn with EtOH & chlorpropamide • rifampin, SJW ↓effect	**Hypoglycemia**: most: chlorpropamide & glyburide (see note below); **least**: tolbutamide, gliclazide,[37] glimepiride[38,39] **Require consistent food intake** to avoid problems with hypoglycemia (↑risk: elderly, debilitated, malnourished) If SU overdose consider IV dextrose & possibly octreotide. Wafarin with glipizide or glimepiride: ↑ hypoglycemia.
Glimepiride AMARYL, g ✗ ⊗ 1,2,4mgˢ tabs	1-2mg daily in AM (8mg daily)	1mg daily 2mg daily 4mg daily	67 67 67	Peak = 2-3h Dur = 24h	↓	↓	↓↓ 1-1.5	-	-	-	↑1.6kg ADOPT 4YR		**AE: Wt gain,** headache, dizziness, **sulpha** skin rx (rash/ photosensitivity [~1%]),GI AE [1-3%], tooth discolour [kids-glyburide] Concern: cardiac [toxicity], hyperinsulinemia, ↓ Na^+ & G6PD.
	Glimepiride/Pioglitazone DUETACT **USA**												Breast milk conc likely minimal with glyburide & glipizide.[Glatstein09]
Glyburide PL DIABETA, g 2.5, 5mg tabsˢ	1.25-2.5mg daily (7.5-10mg BID $35)	5mg po daily-BID 7.5mg BID ADOPT Peds: 0.05-0.45 mg/kg/d	18-23 29	Onset ≤ 60min Peak = 2-4h Dur = 12-**24h**									Combo agent in USA only: glimepiride/pioglitazone DUETACT
Tolbutamide PL ORINASE, g 500mg tabˢ	250mg daily (1000mg TID)	500mg po BID 500mg po TID	34 **46**	Peak = 3h Dur = 6-**12h**									
Meglitinides (GTN) – short-acting insulin secretagogue; bind to β cell to stimulate insulin release at different site than SUs; (adjust dose at ~7days); usually D/C if on insulin (?Option: HNF1A-MODY)													
Nateglinide PL STARLIX ☎ ▼ 60, 120mg tab: D/C by co	60mg TID ac [Navigator NS] (180mg po TID)	60mg po TID 120mg po TID	194 194	O ≤ **20min** P =60-120min D ≈ **4h**	↓	↓↓	↓ **0.5**	-	-	-	-/↑	•CYP [3A4] inhib [↑ effect: Amiodarone, azole-[antifungal], cipro, clari-/ery-thromycin, cyclosporine, diltiazem, gemfibrozil & PI [HIV meds.] •CYP [3A4 inducer] ↓ [effect]: barbs, CBZ & rifampin •CYP [2C8 inhib.]: clopidogrel, TMP	Restores 1st phase insulin release - ↓ PPG Rapid, short duration ⇒ May ↓ risk of hypoglycemia vs SUs ∴option in elderly; **{Flexibility with food intake: skip dose if skip meal; take extra dose if add meal}** If stopping other hypoglycemics, begin next day & watch for hypoglycemia. **ROLE**: alone or + MF, TZD, or insulin Agents lack outcome data on morbidity &mortality.
Repaglinide PL GLUCONORM,g ☎ ▼ 0.5, 1, 2mg tab	0.5mg TID ac {if no prev tx or A1C <8%} (4mg QID)	0.5mg po TID 1-2mg po TID 4mg po TID	**120/44** g 240/81g	O =15-60min P =60-90min D ≈ **4-6h**			↓↓ 1-1.5						
Thiazolidinediones (TZDs) (aka "glitazones") – Insulin Sensitizers: ↓ hepatic output of glucose & ↑ peripheral insulin uptake; ~4-6+ weeks before effect (adjust dose at ~2 months)													
Pioglitazone PL **ACTOS, g** ☎ ✆ 15, 30, 45 mg tab	15mg daily (45mg/day [ACT NOW])	15mg po daily 30mg daily [PERISCOPE] 45mg daily [PROACTIVE,IRIS, NASH]	52 g,279 69 g,**379** 99 g,555	**Delayed action…** Onset ≥ 4 wks **Max effect in 8-16 wks**	↑ macular edema; FDA'11: >1yr use may ↑ bladder ca						↑↑ ↑3.6kg PROACTIVE 3yr	• Cholestyramine ↓ absorption ~70% • Hepatic CYP [2C8] • ↑ by gemfibrozil , abiraterone; & ↓ by rifampin • Pioglit (not rosi-) CYP [3A4] weak/moderate inducer so may ↓ OCPs	More effective in obese or hyperinsulinemia pts **Hypoglycemia with combo-therapy but not monotherapy** Ovulation resumption possible in anovulatory ♀ [premenopausal PCOS.] **CI**: any HF; triple tx [?MF+SU+ TZDs.] **AE: Edema 4.8%** (**HF 2x** [40,41];HTN);**↑Wt**; anemia [~1% mild] (due to hemodilution?);↑fractures [esp ♀ 2X]; monitor **liver fx (ALT)** when indicated **ROLE**: +MF/SU [/DPP if MF CI]; ↑HF if with insulin. Rosi: ↑MI risk**??** [60] Rosiglitazone FDA Dec'15: no longer REMS requirement. Pioglitazone may have more +ve lipid effect [42,43]
Rosiglitazone [1st approved 2000] PL **AVANDIA** ☎ ✆ 2, 4, 8mg tab	4mg daily {4mg max if with SU} (4mg BID) BID dose ~more effective [44]	4mg daily 4mg po BID ADOPT 8mg daily [DREAM, RECORD] Europe D/C Sep'10	**246** **462** CDN **339** [FDA:REMS] **Restricted no longer –Dec 2015.**		↓	↓	<1 or 1-1.5	45,46 -/↑	47,48 ↑	-/↓	↑↑ ↑4.8kg ADOPT 4yr		
Metformin/**Rosiglitazone** **AVANDAMET** ☎ ⊗ 500mg/**1mg**, 500mg/**2mg**, 1000mg/**2mg** 500mg/**4mg**, 1000mg/**4mg**		1000mg/2mg po BID 1000mg/4mg po BID	284 377		?? May ↑MI, CV risk [Nissen, DREAM?, FDA]; ↑ Macular edema; advise against using rosi ADA'08								
α Glucosidase Inhibitors –inhibit α-glucosidases in brush border of small intestine; prevent hydrolysis & delay carbohydrate digestion (Tx hypoglycemia with glucose tablets [Dex4], honey or milk; [sucrose not absorbed])													
Acarbose PL **GLUCOBAY** (prev **Prandase**) 50, 100mg ˢ tabs	**25mg daily** (100mg TID) [STOP-NIDDM 49]	50mg po TID cc 100mg po TID cc	99 **133**	**Meal-time dosing;** ~8 wks for max. effect	↓	↓↓	↓ 0.5-0.8	-	-	-/↓	-/↓	• ↓ digoxin effect • Cholestyramine & cathartics ↑ effect •Enzymes [amylase/pancreatic] ↓ effect; •↓ Fe^{++}?	**AE: GI intolerance (flatulence >41%, diarrhea >28%)**; ↑ LFTs [3%] & hepatic failure. Accumulation in ↓ renal fx. Avoid in chronic GI disease. (Low hypoglycemia risk.) **↑ dose q4-8wks. ROLE** minimal: if **↑PPG**; + SU, MF; (+Insulin?)
					acarbose minimally absorbed; monitor 2hr PPG								

OPIOID TAPERING – *when reducing or discontinuing an opioid in chronic non-cancer pain (CNCP).*

Loren Regier © **www.RxFiles.ca** Mar 2017

A) General Considerations

1) Determine if the goal of dose reduction is reasonable (e.g. opioids have demonstrated some benefit) or if complete discontinuation is more suitable (e.g. trial has been highly problematic/ineffective, opioid induced hyperalgesia is a concern, or patient is addicted & at very high risk).
2) If goal is to reduce dose, option to taper further & more gradually may be considered at a later point. Tapering plan may be paused/reassessed at any point if pain/function deteriorates or withdrawal symptoms persist. However, the "hold off on further taper & plan to restart taper" conversation should have a designated endpoint and be one conversation, not two!
3) Gradual tapers can often be completed in the range of 2 weeks to 6 months. However, some may benefit from a longer time frame of 18 to 24 months. Literature varies widely.
4) **Initial daily dose reductions in the range of 10-20% every 1-2+ weeks may be reasonable.[1] Once 1/3 of the original dose is reached, smaller dose reductions (e.g. 5-10% every 2-4+ weeks) may be more optimal for a successful taper.[1] (May require formulation change).**
5) Formulations that offer smaller dose increments are useful for more gradual tapers once in the lower end of the dosage range. {Examples: morphine long-acting: M-Eslon 10mg cap $_{q12h}$, KADIAN 10mg or 20mg cap $_{q24h}$}
6) More rapid tapers are possible & sometimes desired. In such cases, use of an opioid withdrawal scale (OWS) & corresponding protocols may be recommended, allowing for successful withdrawal within 1-2 weeks. (See links)[2,3]
7) Given the complexities in some cases, discussion with experienced colleagues and an interdisciplinary approach will help optimize management. Continue to use "best practice" tools (e.g. functional assessment, *Opioid Manager* from Canadian guidelines, urine drug screens, etc).

PATIENT MANAGEMENT

1) Anticipate withdrawal effects & have a plan to manage.

2) Optimize other pain management (e.g. non-drug; addition of co-analgesics for neuropathic pain such as nortriptyline, duloxetine, gabapentin or pregabalin).

3) Encourage functional goal setting and efforts to enhance non-drug approaches in management plan.

4) Strongly caution patients that a) they have lost their tolerance to opioids after as little as a week or two of abstinence, and b) they are at risk for overdose if they relapse/resume their original dose.

B) Timeline & Tips for Stopping or Tapering e.g. to Target Dose of <50 or <90 MEQ/day

- Allow for gradual q3 day, weekly, bi-weekly or monthly dose reductions. Reassess as necessary. In general, the higher the dose & longer the duration of previous opioid therapy, the more time should be allotted for tapering.
- Consider ***cross-over rotation taper.*** Eg. Switch to alternate opioid at 50-60% equivalent dose. The lower dose accounts for incomplete cross tolerance. Slowly up-titrate new opioid to ~50% dose while gradually tapering off previous opioid.
- Tapering the last 20-60 mg (morphine equivalent) may require more time.

C) Opioid Withdrawal Symptoms (See table to the right.)

- **Many of these symptoms may not be seen with a gradual taper!**
- Physical withdrawal symptoms generally resolve over 5-10 days.
- Psychological withdrawal symptoms (dysphoria, insomnia) may take longer.

EARLY symptoms may include:	LATE symptoms may include:	PROLONGED symptoms may include:
- anxiety / restlessness - sweating - rapid short respirations - runny nose, tearing eyes (minor) - dilated reactive pupils	- runny nose, tearing eyes - rapid breathing, yawning - tremor, diffuse muscle spasms/aches - pilo-erection - nausea and vomiting; diarrhea - abdominal pain - fever, chills - ↑ white blood cells (if sudden withdrawal)	- irritability, fatigue, psychological - bradycardia - decreased body temperature
Early = hours to days **Late** = days to weeks **Prolonged** = weeks to months		◆ Some people with chronic pain will find that symptoms such as fatigue and general well-being improve over time with tapering of the opioid. In such cases, gradual gains in function will be possible & should be explored.

D) Management of Other Withdrawal Related Side Effects

Aches/Pains/Myalgia:

⇨ **NSAID** (e.g. naproxen 375-500mg twice daily or ibuprofen 400-600mg four times daily)**:** useful for pain & withdrawal. **(Give regularly initially.)**

⇨ **Acetaminophen** (650-1000mg every 6 hours as needed) may be used for *aches, pains, flu-like symptoms.*)

Bowel Function (Constipation / Diarrhea):

⇨ **Laxative** - continue initially to prevent constipation; with time, reduce, hold & eventually stop laxative (See RxFiles Opioid Induced Constipation, page 61)

⇨ **Loperamide** - used if necessary for *diarrhea*; may not need with gradual taper.

Nausea/Vomiting:

⇨ **Dimenhydrinate** 50-100mg q6 hours as needed [More effective alternatives: **prochlorperazine** 5-10mg po q6-8h; **haloperidol** 0.5-1mg po q8-12h]

Anxiety, Irrritability, Lacrimation, Cramps, Rhinorrhea, Diaphoresis, Insomnia:

⇨ **hydroxyzine** 25-50mg po TID PRN, or sometimes just needed at HS (short-term)

Insomnia:

⇨ **Employ non-drug & sleep hygiene measures** (e.g. CBT, regular bedtime & wake-time; sleep restriction).[4,5,6] If short-term pharmacologic tx necessary, options: **trazodone** 25mg po HS [$12] up to 100mg; **amitriptyline** 10mg po HS [$13], **doxepine** SILENOR 3-6mg po HS [$30-50].

Physical Withdrawal Symptoms (general):

⇨ **Clonidine 0.1mg twice daily may be prescribed for general relief/prevention**. Initial test dose 0.1mg x1; check BP & HR 1 hr later (if BP <90/60, postural hypotension, or HR <60, do not prescribe further). May titrate up to 4x/day. Reassess in 3-7 days; taper, over ~7-10 days, to stop. [Cochrane review documented typical clonidine use for 7-14 days; longest duration was for 30 days.[7]] Clonidine not routinely needed if gradual opioid taper. However there is some evidence that it may ↑ duration of abstinence decoupling stress from craving.[8]

Sweating: ⇨ **Oxybutynin** 2.5-5mg po BID PRN (short-term)

See also the RxFiles Opioid Tapering Template - version of this document, online.
http://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Taper-Template.pdf

INFLAMMATORY BOWEL DISEASE: Drug Comparison Chart

Originally prepared by A Lindblad PharmD; L Regier BSP BA, B Jensen BSP Mar 2017

GENERIC/TRADE (Strength & formulations)	THERAPEUTIC USE/ COMMENTS	CONTRAINDICATIONS CI/ ADVERSE EVENT AE/ DRUG INTERACTIONS DI/ MONITORING M	ACTIVE DISEASE & MAINTENANCE DOSE [23,24, 25, 26]	$/ MONTH
PURINE ANTIMETABOLITES (Thiopurines) ⇨ Time to effect: 3-6 months. May tolerate mercaptopurine if intolerance (e.g. hepatotoxicity or arthralgia/myalgia) to azathioprine.				
AZATHIOPRINE AZA IMURAN, g 50ς mg tab dumbbell shape (Can make susp) 50mg/17 mL vial; -prodrug of 6MP	✓mod-severe UC ? & CD for pts not responding/unable to wean from po steroids (maintain steroid induced remission) -useful in fistulating CD. -may ↓ post-op recurrence in CD [115], but only in smokers [387]; use if high-risk for recurrence -educate pts on sx pancreatitis; pancreatitis reappears on re-challenge; ↑ risk with smoking. Pregnancy: no harm vs matched-IBD controls.[187] ? risk of neonate immunosuppresion if exposed during 3rd trimester & ? ↑ infant infections at 9-12 months with thiopurine + anti-TNF-α vs anti-TNF-α monotherapy; ↓ dose if possible.	AE: flu-like fever (after ~2-3 wks tx), bone marrow suppression 2-5%, dose dependent, unpredictable (esp. leukopenia), infection PML, **hepatotoxic** 2%, allergy<5%, pancreatitis (as hypersensitivity rxn 2% within 1st 3-4wk) nodosum, ?lymphoma, [111] ?↑nonmelanoma skin CA;[184] GI dose-related & ↓with time DI: **allopurinol/febuxostat** (↑↑ levels/toxicity) may ↓ 6MP dose by 75% & titrate allopurinol, [186] ↑ infections with steroids; ACEI/BACTRIM may ↑ leukopenia/ anemia; live vaccine; anti-TNFs may ↓ **antibodies** {5-ASA, sulfasalazine & olsalazine may inhibit TPMT enzyme M: CBC every other week while adjust dose, then q1-3month; LFTs; (If ↑plasma level &/or ↓**TPMT genotype** 6/ 1000, esp. African-Caribbean pts have ↑↑ level & AEs, but routine monitor of limited value;[174] vs routine pt/other blood work follow up)	Start at 50mg once/day & ↑ by 25mg q1-2wks until target **UC**: 1.5-2.5mg/kg/day [150] 50-100mg po daily **CD**: 2-3mg/kg/day [28] (Sonic 2.5mg/kg) [132] 150mg po daily **CD Peds**: 2.5 mg/kg/day (Cinn); {in RA: 0.1mg/kg/day, ↑ by 0.5mg/kg/day up to 2.5mg/kg/day} AZA & 6MP: Maintenance dose same as induction dose	$18-27 $34
MERCAPTOPURINE 6MP PURINETHOL, g 50ς mg tab round ♣ ☎▼: Crohn's			Start at 50mg once/day & ↑ by 25 mg every 1-2wk until target UC & CD: 1 TOPPIC-1.5 mg/kg/day; 50-75-100mg po daily CD Peds: 1.5 mg/kg/day (Cinn)	$104-202
BIOLOGIC RESPONSE Modifier (Anti TNF-α Monoclonal Antibody) ⇨ Time to Effect: 2 weeks (ACT). Anecdotal: may start to see benefit within few days. Endoscopic remission "mucosal healing" observed!				
INFLIXIMAB INF REMICADE; INFLECTRA☎ℰ g REMSIMAχ⊗ g; 100mg vial inj ♣ ☎ℰ: CD & UC Consider D/C gestational wk 30-32. Reports of newborn neutropenia-?monitor ANC[328] -a chimeric monoclonal antibody Etanercept ENBREL - **not** effective[38]	-used in mod-sev UC ACT-1,2 & CD ACCENT-I,II; Sonic unresponsive to standard tx; in UC: INF + AZA > monotx for inducing steroid-free remission unpublished abstract [183]; promote mucosal healing. -used in mod-sev or fistulating disease in hospitalized pt req. rapid onset; as a bridge to immunomodulator; or to ↓ extra-intestinal manifestations of CD (erythema nodosum; pyoderma gangrenosum) -concomitant use AZA/6MP, MTX can ↓ formation of antibodies ? benefit -also ↓ response in smokers[2] -taper steroids if achieve remission.	CI: infection (active TB, serious/opportunistic fungal, Hep B); optic neuritis; demyelinating disorders e.g. MS, HF NYHA class 3-4; recent CA AE: infections, infusion reactions with IV ~10% (headache, dizziness, flushing, fever, chills, chest pain, cough, dyspnea & pruritis), nausea, abdominal pain, fatigue, rash; delayed reactions (3-14 days post-infusion; serum-sickness like). Stop if jaundice or ↑↑LFTs. -**Pretreat** infusion (acetaminophen 650mg & diphenhydramine 50mg po x1); ↓'s reactions. Give over ≥ **2**-4hr in 250mL normal saline infuse ≥1hr if tolerated long term -Severe AE more frequent in peds: ↑ **LFTs**, anemia, infection, flushing, blood dyscrasias, fractures, acute reaction -Rare lymphoma (rates unknown; estimate of **lymphoma 2/1000** & **mortality 4/1000** in CD **at 1 year**), drug-induced lupus, melanoma[29] DI: abatacept, anakinra, live vaccines (may ↑ infections); MTX may ↑ adalimumab level M: baseline tuberculin test, symptoms of infection e.g. shingles/PHN, candidia. q8-12wks: urinalysis, CBC, etc. LFTs q2wks x2mos, then q8-12wks. -CDN guide: ↑dose first; trough may be important	**Active CD & UC**: 5mg/kg/dose over 2hr {Some use of higher doses ≤10mg/kg} (Age ≥6yr: CD in USA & ≥9yr in CDN; UC in CDN/FDA} at wk 0, 2, 6 -if no response after 3 doses, stop drug **Maint CD & UC**: 5mg/kg/dose q8 weeks -some evidence for "PRN" dosing, rather than regular dosing -If respond initially & then lose response: ↑ frequency to q4weeks OR ↑dose to 10mg/kg q8weeks - ↓/taper corticosteroid?	300mg IV x 3 doses (~5mg/kg x 60kg) Week 0, 2, & 6 300mg IV q8wks (~5mg/kg x 60kg) 600mg IV q8wks (~10mg/kg x 60kg)	$5,900 g, $8,815 (3 doses) $11,900 g, $17,750 (1 year) $23,600 g, $35,315 (1 year)
ADALIMUMAB HUMIRA ☎ℰ 40mg inj pen	-use: RA, JRA age ≥4yr CDN;FDA≥2yr PsA, psoriasis plaque, ankylosing spondylitis, CD ≥ 13yr CDN;FDA≥ 6yr, UC mod-sev adult (human antibody)			**Induction:** 160mg wk 0, 80mg wk 2 **Maintenance:** 40mg SC q other wk	$19,610 (1 year)
CERTOLIZUMAB PEGOL CIMZIA χ⊗ 200mg syr (29g needle new)	-use: mod or severe adult CD FDA, mod-severe RA, AS, adult active PA (humanized Fab fragment TNF antibody) -agent does not cross the placenta			**Induction:** 400mg SC q2wk x3 **Maintenance:** 400mg SC q4wk	$17,630 (1 yr/ 13 doses)
GOLIMUMAB SIMPONI☎ℰ 50 & 100mg syringe/auto-inj	-uses: RA with MTX, psoriatic arthritis, ankylosing spondylitis; mod-severe adult UC FDA May'13, CDN Sep'13 PURSUIT studies for UC			**Induction:** 200 mg wk 0, 100mg wk 2 **Maintenance:** 50-100 mg SC q4wk	20,500/yr
Ustekinumab STELARAχ⊗	mod-severe adult CD CND&FDA'16: fail immunmodulator/steroid; PP&PsA☎; IL 12/23ɵ	AE: candidiasis, pruritus, UTI/TB, hypersensitive rx, ?cancer/leukoencephalopathy; DI	Mod to severe active CD	260-520mg IV LD, **then** 90mg SC q8-12wk	30,000/yr
Vedolizumab ENTYVIO χ⊗	mod-severe UC/CD CDN + CD FDA'14, integrin receptor ɵ antibody	AE: HA, nausea, joint pain, fever, infection ?PML, hypersensitive rx, ↑LFT.	Mod to severe active UC	300mg IV over 30min at 0, 2, 6, then q8wk	27,600/yr
OTHER					
METHOTREXATE, g 2.5ς & 10mg tabs; (20 & 50mg/2mL inj χ▼) Dihydrofolate reductase inhibitor D/C ≥90 days prior → PL	-CD when not responding to AZA/6MP -insufficient evidence for UC **Time to Response:** 4 wks {evidence for parenteral form; no not as effective} [30] -Consider **folic acid** supplementation (1mg/day or 5mg/wk)	CI: pregnancy, breastfeeding, liver disease AE: leukopenia, GI, HA, dizzy, fatigue, thrombocytopenia, rash, cough, photosensitive, alopecia, stomatitis, & reversible sterility in men Rare: hepato/nephro-toxicity, SJS, hypersensitivity pneumonitis 3 cases/100 pt yr [31] DI: BACTRIM ↑ myelopsuppression, alcohol, live vaccine, cyclosporine, anti-TNF's may ↓ antibody, NSAIDs may ↑ MTX level M: CBC, liver indices, SCr, albumin at baseline & within 4 wks of starting therapy, then q month; ?annual CXR [32]	**CD**: 25mg SC/IM weekly (or po? 70% bioavailable) 15-25 mg IM weekly; can use 25 mg IM weekly for 16 weeks followed by 15 mg SC/IM weekly **Peds CD**: 15 mg/m² SC/IM weekly (up to 25 mg); {wk 1: 50% of dose; wk 2: 75% dose; wk 3: 100% of dose}; [33] once steroid stopped & pt stable, ↓ dose by 20%, further ↓ by 20% in another 3-6 months if stable [32]	$70 IM/ $37 po $70
METRONIDAZOLE FLAGYL, g 250mg tab; 500mg cap ▼↑s; 500mg IV P_1,$P_{2,3}$ L Pregnancy: consider Amox/Clav PL	-vague role; add to 5-ASA or steroids when ineffective alone; helpful in ruling out GI infection; ? helpful in abscesses or fistula & disease limited to perianal dx -no benefit combined with IV **steroids** ?; still used if Sx persist with UC {Often in combo with cipro for 2 wks followed by metronidazole monotx for 2 wks Opinion}	AE: nausea, metallic taste, HA, dry mouth, furry tongue; ?CA, ataxia, peripheral neuropathy with long-term use (often not reversible) DI: alcohol (disulfiram reaction), warfarin (↑ bleeding)	10-20mg/kg/d in divided doses; 500mg po/IV BID	$18 / 170
CIPROFLOXACIN, g 250, 500 & 750mg tab; 500mg & 1g XL ⊗; 200, 400mg IV; 100mg/mL susp PL → Use after 1st trimester	-used occasionally; may be used in conjunction with or in place of metronidazole	AE: somnolence, dizziness, rash, GI N/V/D, arthralgias, photosensitive, rare tendon rupture DI: cations++, glyburide, mirtazapine, QTc prolonging drugs, tizanidine & warfarin	500 mg po BID >90% oral bioavailability 400 mg IV q12H	$56 $1010
CYCLOSPORINE, g CsA NEORAL, SANDIMMUNE (IV) 10, 25, 50 & 100mg caps; 100mg/mL oral susp; 50mg/mL (1 & 5 mL vials) ☎ℰ (not IBD in SK)	-Rare!; severe UC to bridge to thiopurine (e.g. surgery-sparing in acute tx of severe, steroid-refractory UC) -not well studied in CD; rarely use > 3-6 months -add to IV hydrocortisone after 7-10 days if no response; concomitant IV steroids recommended Tech; withdrawal may lead to Sx recurrence; consider PJP prophylaxis **[Generally avoided given newer agents!]**	AE: ↑BP, consider amlodipine tx; paresthesias, HA, abnomal LFTs, hyperkalemia, gingival hyperplasia, hypertrichosis, tremor; nephrotoxicity Rare: infection, seizure; ?lymphoma, [32] anaphylaxis **Time to Response:** 2-3 weeks [32] DI: many! M: CBC, lytes, SCr, LFTs?, CsA levels, BP; baseline Mg++ & ?cholesterol **Target trough concentration**: unknown; 200-800 ng/mL (via monoclonal radioimmunoassay) or 200-400 ng/mL (via HPLC) [2]; 150-300 ng/mL [34,Romano]	**UC**: 2mg/kg/day IV infusion for 7-10 days, 150mg IV/d x 10day Switching to Oral: taper steroids & start AZA/6MP prior to change & continue for maintenance; ? temporarily stop AZA if starting CsA [32,35] {If serum Mg++ low, reduce dose of CsA} {Tapering: start 5-8 mg/kg/day given po BID for 1–3 months [32]} NEORAL > SANDIMMUNE for bioavailability 150mg po q12h	$165 (10 days) $540

☎=Exception Status SK χ=Non-formulary SK ℰ=prior NIHB ⊗=not NIHB =↓dose for liver dysfunction =↓dose for renal dysfx ς=scored **5-ASA**=5-aminosalicylic acid **6MP**=mercaptopurine **AE**=adverse effects **ANC**=absolute neutrophil count **AZA**=azathioprine **BMD**=bone mineral density **CA**=cancer **CBC**=complete blood count **CD**=Crohn's **CSA**=cyclosporine **dx**=disease **EC**=enteric coated **ESR**=erythrocyte sedimentation rate **GI**=stomach **HA**=headache **Hgb**=hemoglobin **Hct**=hematocrit **MS**=multiple sclerosis **MTX**=methotrexate **OP**=osteoporosis **po**=orally **pr**=rectally **SSZ**=sulfasalazine **supp**=suppository **UC**=ulcerative colitis **yr**=year

Not in Canada: **Balsalazide COLAZOL** FDA: UC ≥5yrs. **Tacrolimus** (FK506): low bioavailability, 0.05 mg/kg BID (target serum concentration: 10-15 ng/mL); mainly open-label, small trials; AE: HA, ↑SCr, ↑BUN, insomnia, leg cramps, tremors, parasthesias. **MMF:** inadequate efficacy evidence, safety concern. **Natalizumab TYSABRI:** 300mg IV q4wk, ↑caution after 193 cases fatal progressive multifocal leukoencephalopathy (PML) in MS (↑risk if JC Ab ⊕); ↑LFT. Restricted USA for Crohn's & MS; MS in Canada 2006. **SPD476:** once daily formulation of 5-ASA-effective at inducing remission in preliminary studies. **Transdermal nicotine** ≥21mg/day (UC): benefits mainly ex-smokers, not as effective as 5-ASA; long-term AE unknown. APRISO: **once daily** mesalamine granule; mild-mod maint. UC (1.5g= 4 cap daily); pH dependent coat around matrix core; released distal ileum & colon; has aspartame. **UCERIS:** FDA'13 Budesonide 6.9mg ER tab DAILY in am for acute UC terminal ileum & colon ≤8wks.

ALTERNATIVE THERAPIES: Acupuncture & wheatgrass. **Probiotics**: Inducing remission in mild-mod UC: 1 small, controlled, open-label trial with **VSL#3**: lactobacilli, bifidobacteria, Strep. Salivarius (3600 billion CFU daily x 8 wks); maintaining remission: ***E. coli* strain Nissle 1917** (200mg daily) **& Lactobacillus GG** effective; small, placebo-controlled trials suggest benefit in preventing pouchitis and preventing relapse of pouchitis; various dosing regimens used in trials. Further data on efficacy & safety needed before routine use;[36] caution if on immunomodulators. Other probiotics: further evidence on efficacy and safety needed, but results look promising. Concerns with lack of live bacteria in some products. **Omega 3s**: insufficient evidence to support/refute; benefit mainly with enteric coated capsules for maintenance of remission in CD [37, 38, 39] **Other**: Avoid food triggers (varies for different patients) i.e. lactose deficiency. ? endometriosis ↑ IBD risk[190]

Factors associated with relapse after stopping: a) AZA/6MP: ♂ UC, extensive dx UC, ↓ duration of remission prior to D/C UC,CD, endoscopy active UC,CD, ↑platelet count CD, ↑CRP CD, ↑WBC/neutrophils CD, ↓ Hgb CD, ↓ duration free of corticosteroids.
b) biologic (infliximab): endoscopically active dx CD, short duration of remission CD, ↑CRP CD, adequate trough levels CD, post-operative CD [Concern that after stopping any of the above, re-induction of remission may be difficult ∴ no clear guidance.]

OBJECTIVE COMPARISONS FOR OPTIMAL DRUG THERAPY

RxFiles Academic Detailing assists physicians, nurse practitioners, pharmacists and other healthcare professionals in making the best possible drug therapy decisions for patients. We weed through the maze of evidence and opinion to consider **effectiveness**, **safety**, **cost**, **patient / societal values** & **other practical considerations**.

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DRUG COMPARISON CHARTS 11TH EDITION

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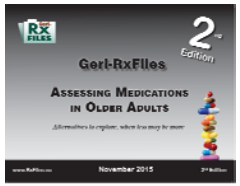

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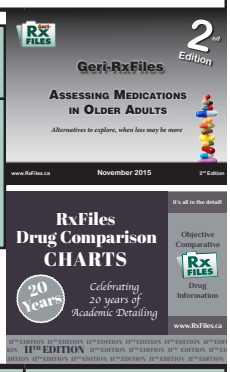

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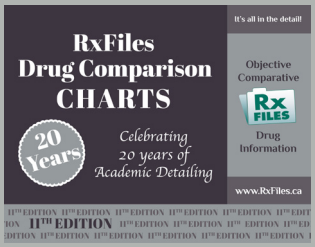

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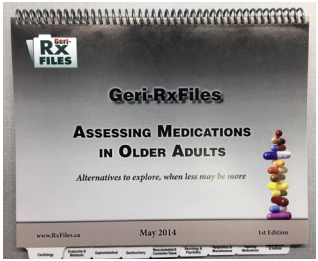

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