Pharmacology of Oral Hypoglycemics

Drug	Initial and (Max.) Dose	Cost (per tablet)	Efficacy	Onset	Kinetics	Interactions	Side Effects	Monitoring
SULFONYLUREAS (SU) stimulate insulin release from beta cells								
Chlorpropamide (Diabinese®)	100 mg daily (500 mg daily) Dose titration q 1-2 weeks. Take 15-30 min before meals Do not use if severe renal or liver disease	Covered by ODB & ADB 100 mg = $ 0.05, 250 mg = $ 0.042	▪ ↓ FPG (~2-3 mmol/L) ▪ ↓ PPBG ▪ ↓ A1c 1-1.5% ▪ Failure rates ~5-10%/year ▪ **<u>Not recommended</u>** due to ↑ BP and ↑ retinopathy (UKPDS-33)	P =3-6 h D = 24-72 h	▪ T ½ = 36 h ▪ Liver met to hydroxylchlorprop-amide ▪ ? active metabolites ▪ Renal excretion depends on pH (↓ with acid)	▪ ↑ Hypoglycemic effect with: salicylates, sulfonamides, MAOIs, **EtOH** ▪ Beta blockers may mask hypoglycemia ▪ Disulfiram like rxn with EtOH (mainly chlorpropamide; 3TC®, Kaletra®, Norvir® oral solutions also contain ETOH) ▪ Rifampin ↓effect	▪ **Weight gain** (may be more with glyburide) ▪ Hypoglycemia (most with chlorpropamide and glyburide; **least:** tolbutamide, glimepiride, & gliclazide) ▪ Nausea, abdominal pain, vomiting, epigastric fullness, diarrhea or constipation, heartburn ▪ Dizziness, headaches ▪ Skin rashes (~1%) ▪ SIADH (hyponatremia) ▪ Leukopenia, thrombocytopenia, mild anemia, aplastic anemia (rare) ▪ Cholestatic jaundice ▪ Antiplatelet effect (gliclazide)	▪ FBG (target 4-7 mmol/L) ▪ A1C q 3-6 months (target ≤ 7%) ▪ S/S hypo or hyperglycemia ▪ Closely monitor elderly, debilitated, malnourished patients or those with renal-liver dysfunction or during stress-illness
Glyburide (Diabeta®)	1.25-2.5 mg daily – administer bid if > 10 mg (10 mg bid) Dose titration q 1-2 weeks. Take 15-30 min before meals	Covered by ODB & ADB 2.5 mg = $0.04 5 mg = $0.07	▪ ↓ FPG (~2-3 mmol/L) ▪ ↓ PPBG ▪ ↓ A1c 1-1.5% ▪ Failure rates ~5-10%/year ▪ **1st choice option for lean patient**	O = 15-60 min P=2-4 h D=12-24 h	▪ T ½ 10 h ▪ Liver metabolism to 4OH glyburide which is active (decrease elim if renal failure) ▪ 50% renal, 50% biliary elimination			
Gliclazide (Diamicron®) (Diamicron MR®)	40 mg daily (160 mg bid) 30 mg daily (120 mg daily) Dose titration q 1-2 weeks. Take 15-30 min before meals	Not covered by ODB Covered by ADB (except MR tab) 80 mg = $0.28 30 mg MR tab= $0.75	▪ ↓ FPG (~2-3 mmol/L) ▪ ↓ PPBG ▪ ↓ A1c 1-1.5% ▪ Failure rates ~5-10%/year ▪ **1st choice option for lean patient**	O = ~60 min P = 4-6h D = 12-24 h	▪ T ½ 10h ▪ 80% renal excretion			

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Drug	Initial and (Max.) Dose	Cost (per tablet)	Efficacy	Onset	Kinetics	Interactions	Side Effects	Monitoring
Glimepiride (Amaryl®)	1-2 mg once daily (8 mg) Dose titration q 1-2 weeks. Take 15-30 min before meals	Not covered by ADB. 1 mg = \$0.49 2 mg = \$0.49 4 mg = \$0.49	▪ ↓ FPG (~2-3 mmol/L) ▪ ↓ PPBG ▪ ↓ A1c 1-1.5% ▪ Failure rates ~5-10%/year ▪ **1st choice option for lean patient**	P = 2-3 h D= 24 h	▪ T ½ 5 - 9 h ▪ Metabolized in the liver; metabolites excreted in urine and feces			
Tolbutamide (Orinase®)	250 mg daily (1000 mg tid) Dose titration q 1-2 weeks. Take 15-30 minutes before meals	Covered by ODB & ADB 500 mg = \$0.08	▪ ↓ FPG (~2-3 mmol/L) ▪ ↓ PPBG ▪ ↓ A1c 1-1.5% ▪ Failure rates ~5-10%/year	O= < 1 hr P =3-4h D = 6-12 h	▪ T ½ 7h (3-28h) ▪ >90% metab. by CYP2C9			
BIGUANIDES increase insulin sensitivity and cellular glucose uptake & utilization; reduce hepatic glucose production; **↓ morbidity & mortality in obese patients** (UKPDS-34)								
Metformin (Glucophage®)	250 – 500 mg daily (850 mg tid) Titrate slowly to minimize diarrhea (q 2-4 weeks) If daily dosing, given with largest meal of the day **Caution if CrCL < 60 mL/min** **Avoid if CrCL < 30 mL/min**	Covered by ODB & ADB 500 mg = \$0.12 850 mg = \$0.21	▪ ↓ FPG up to 3 mmol/L ▪ ↓ PPBG ▪ ↓ A1c 1-1.5% ▪ Positive effect on lipids (↓ TG & TC, ↑ HDL) ▪ **DOC for patients with BMI ≥25** ▪ **Useful for prevention of DM in patients with glucose intolerance**	O =~ 1 h, P = 2-3 h D = 8-12 h max. effect ~14 days	▪ no liver metabolism ▪ no metabolites ▪ renal elimination by GFR & TS ▪ T ½ 3-6 h	▪ EtOH and cimetidine ↑ effect ▪ Stop metformin 48 hours before IVP dye & do not restart until renal function has been re-evaluated ▪ In patients at risk of/already experiencing mitochondrial toxicity (esp. secondary to prolonged NRTI use), use with caution due to risk of hyperlactatemia or lactic acidosis	▪ NOT associated with hypoglycemia or weight gain like sulfonylureas ▪ GI ++++ ▪ Diarrhea (dose related ~30%) ▪ Anorexia ▪ Lactic acidosis (1:10000, avoid if liver-renal-cardiorespiratory insufficiency or alcoholism, receiving IVP dye or undergoing surgery) ▪ Metallic taste 3% ▪ Asymptomatic ↓ B12 but not typically associated with anemia	▪ FBG (target 4-7 mmol/L) ▪ A1c q3-6m (target ≤ 7%) ▪ S/S hypo or hyperglycemia ▪ Renal function

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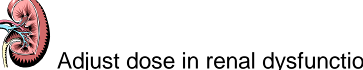
Metformin/ Rosiglitazone (Avandamet®)		Not covered by ADB. 500 mg/1mg = $0.63 500 mg/2 mg = $1.14 500 mg/4 mg = $2.03 1 g/ 2 mg = $1.24 1 g/ 4 mg = $2.15						
THIAZOLIDINEDIONES (TZDs) insulin sensitizers: ↓ hepatic output of glucose & ↑ peripheral insulin uptake								
Pioglitazone (Actos®)	15 mg daily (45 mg daily)	Covered by ADB 15 mg = $2.18 30 mg = $3.08 45 mg = $4.63	▪ ↓ A1c 1-1.5 % ▪ ↓ FPG ~1-2 mmol/L ▪ may have more favorable lipid effects than rosiglitazone ▪ **ROLE**: combine with metformin, SU	**Slow onset** **Max effect in ≥ 1 month**	▪ Extensive liver metabolism: 2C8, 3A4 >> 1A1 ▪ T ½ 16-24 h	▪ 3A4 inhibitors such as **PIs,** ketoconazole & erythromycin may ↑ effect ▪ CYP inducers (e.g. **NNRTIs, tipranavir**, rifampin, carbamazepine) may ↓ effect ▪ ? may cause OCP failure ▪ Rx that cause hypo or hyperglycemia	▪ Does not cause hypoglycemia by itself ▪ Fluid retention (worsen heart failure or hypertension) ▪ Dose related ↓ Hgb/Hct (appears 4-12 wk then remains stable) – may be caused by hemodilution ▪ Mild weight ↑ (typically due to fluid retention) ▪ May affect menstrual cycle ▪ fatigue	▪ FBG (target 4-7 mmol/L) ▪ A1c q 3-6 m (target ≤7%) ▪ LFTs (q2m x 1 year) ▪ S/S liver failure or jaundice

Drug	Initial and (Max.) Dose	Cost (per tablet)	Efficacy	Onset	Kinetics	Interactions	Side Effects	Monitoring
Rosiglitazone (Avandia®)	4 mg daily (4 mg bid) – bid dose more effective	Covered by ADB 2 mg = $1.29 4 mg = $2.02 8 mg = $2.88	▪ ↓ A1c 1-1.5 % ▪ ↓ FPG ~ 1-2 mmol/L ▪ **ROLE**: combine with metformin, SU	**Slow onset** **Max effect in ≥ 1 month**	▪ Extensive liver metabolism by 2C8	▪ ? may cause OCP failure ▪ Rx that cause hypo or hyperglycemia • Open label single sequence crossover study in healthy subjects (n=14) to evaluate effect of **ATV 400mg** daily and **ATV/r 300mg/100mg** daily on kinetics of rosiglitazone 4mg daily (CYP 2C8 probe). • Rosiglitazone AUC ↑ 35% by atazanavir, while rosiglitazone AUC↓ 17% by atazanavir/r • ATV is a weak inhibitor of CYP2C8, while ATV/r appears to induce CYP2C8 and offset inhibition by ATV[1]		

MEGLITINIDES short-acting insulin secretagogue: bind to beta cell to stimulate insulin release at different site than SUs								
Repaglinide (GlucoNorm®)	0.5 mg tid before meals (if no previous treatment or HA1c <8%) (4 mg qid) Adjust dose after ~ 7 days. Take before meals; if skip meal, skip dose	Not covered by ODB Covered by ADB 0.5 mg = $0.28 1 mg = $0.29 2 mg = $0.30	▪ tid may be superior to bid ▪ RCTs suggest as effective as low dose glyburide (<10 mg) ▪ ↓ A1c 1-1.5% ▪ ↓ FBG ~ 1-2 mmol/L ▪ used to prevent post-prandial hyperglycemia ▪ more flexible than SU –if unable to eat do not take dose ▪ **ROLE:** alone or + metformin, TZD, or insulin	O=30 min P= ~60-90 min D= ~ 4 hr	▪ PB ~98% ▪ Vd ~31 L ▪ Liver metabolism by oxidation & conjug.with glucuronic acid ▪ Inactive metabolites ▪ Renal excretion ~8% ▪ T ½ ~ 1 hr	▪ 3A4 inhibitors such as **PIs,** ketoconazole , gemfibrozil & erythromycin may ↑ effect ▪ CYP inducers (e.g. **NNRTIs, tipranavir**, rifampin, carbamazepine) may ↓ effect ▪ Rx that cause hypo or hyperglycemia	▪ Hypoglycemia ~16% (lower than SUs) ▪ Nausea <5% ▪ Diarrhea <5% ▪ Constipation ~2-4% ▪ Dyspepsia 2-4%	▪ FBG (target 4-7 mmol/L) ▪ A1c q 3-6 months ▪ S/S hypo or hyperglycemia
Nateglinide (Starlix®)	60 mg tid before meals (180 mg tid) Adjust dose after ~ 7 days. Take before meals; if skip meal, skip dose	Not covered by ODB & ADB 60 mg = $0.53 120 mg = $0.53 180 mg = $0.57	▪ RCTs suggest not as potent/effective as glyburide 10 mg or metformin 500 mg tid ▪ ↓ A1C ~ 0.5% ▪ ↓ FPG ~ 0.3 mmol/L ▪ **ROLE:** alone or + metformin, TZD, or insulin	O = <20 min P = 60-120 min D = ~ 4h	▪ PB ~98% ▪ Vd ~ 10 L ▪ Liver metabolism by hydroxylation and glucuronide conjugation ▪ Metabolites less active ▪ Renal excretion ~ 16% ▪ T ½ ~ 1.5 hrs	▪ 3A4 inhibitors such as **PIs,** ketoconazole & erythromycin may ↑ effect ▪ CYP inducers (e.g. **NNRTIs, tipranavir**, rifampin, carbamazepine) may ↓ effect ▪ Rx that cause hypo or hyperglycemia	▪ Hypoglycemia (relatively uncommon ~ 2%) ▪ Adverse effects seen more frequently than placebo: ▪ Upper resp infxn ▪ Back pain ▪ Flu symptoms ▪ Dizziness ▪ Diarrhea ▪ coughing	▪ FBG (target 4-7 mmol/L) ▪ A1c q 3-6 months ▪ S/S hypo or hyperglycemia

α GLUCOSIDASE INHIBITORS inhibit α-glucosidase in brush border of small intestine; prevent hydrolysis & delay carbohydrate digestion								
Acarbose (Prandase®)	25 mg daily (100 mg tid) Take at mealtime. Maximum effect takes weeks; ↑ dose q 4-8 weeks.	ODB limited use ADB covered 50 mg = $0.26 100 mg = $0.36	▪ Modestly effective ▪ ↓ A1c <1% ▪ ↓ Post prandial glucose ~ 3 mmol/L ▪ **ROLE:** useful in patients with ↑ PPBG; with SU, metformin ▪ **Useful for prevention of DM in patients with glucose intolerance**	May take several weeks for maximum effect.	▪ Minimal absorption	▪ Amylase & pancreatic enzymes ↓ effect	▪ Flatulence ▪ Diarrhea ▪ Abdominal cramp ▪ All of the above ~50-75% of patients. Dose related ▪ If in combination with other sulfonylureas or insulin, must teach to **treat hypoglycemia with glucose-based product since acarbose will block absorption of more complex disaccharides** ▪ Increased LFT if >150 mg /day	▪ LFTs if > 150 mg/day q 3 months ▪ FBG (if combo therapy) ▪ PPBG ▪ A1c q 3-6 months ▪ S/S hypo or hyperglycemia especially if combination therapy

Abbreviations: ADB = Alberta Drug Benefit; ODB = Ontario Drug Benefit; PB = protein binding; EtOH = alcohol; FBG = fasting blood glucose; PPBG = post-prandial blood glucose; DOC = drug of choice; O = onset; P= peak; D= duration


Adjust dose in renal dysfunction

1. Sevinsky H, Eley T, Yones C, Persson A, Li T, Xu X, et al. Effect of atazanavir with and without ritonavir on the pharmacokinetics of the CYP2C8 probe rosiglitazone in healthy subjects [abstract O5]. 9th International Workshop on Clinical Pharmacology of HIV Therapy, New Orleans, LA. April 7-9, 2008.