Antihyperglycemic Agents Comparison Chart

Parameter	Metformin	Sulfonylureas	Meglitinides	Glitazones (TZD's)
Mechanism of Action	↓ Hepatic glucose output ↑ Peripheral glucose uptake by enhancing insulin action	↑ insulin secretion (both basal & prandial)	↑ insulin secretion (primarily prandial)	↑ Peripheral glucose uptake by enhancing insulin action ↓ Hepatic glucose output
Efficacy (A1c Reduction)	1 – 1.5 %	1 – 1.5 %	Repaglinide 1 – 1.5 % Nateglinide 0.6 – 1 %	1 – 1.5 %
Hypoglycemia Risk	0	Glyburide ++++ Glimepiride +++ Gliclazide ++	+	0
Weight Change	↓	↑	↑	↑↑
Suitability for use in heart failure	OK in stable heart failure; Monitor renal function; consider stopping metformin if significant reduction in GFR (see above)	OK	OK	Avoid in all stages of heart failure; CDA guidelines state may be used in mild, stable CHF if patient is closely monitored by a specialist
Metabolism & Excretion	• Negligible metabolism • Excreted 100% as unchanged drug by glomerular filtration plus active tubular secretion	Sulfonylureas are extensively metabolized primarily via CYP2C9. Excreted primarily as inactive or weakly active metabolites. • Gliclazide: metabolized to inactive compounds • Glimepiride: metabolized to inactive compounds • Glyburide: metabolized in part to weakly active metabolites that may accumulate in renal impairment	Repaglinide: • Extensively metabolized to inactive compounds primarily via CYP2C8 & to lesser extent via 3A4 • Excreted as inactive metabolites primarily in the bile; very little excreted as unchanged in urine Nateglinide: • Extensively metabolized to inactive compounds primarily via CYP 2C9 (70%) & to lesser extent via 3A4 • Excreted primarily as metabolites; only 15% as unchanged drug in urine	Pioglitazone: • Extensively metabolized to inactive compounds primarily via CYP2C8 & to a lesser extent 3A4; (H) • Excreted as inactive metabolites primarily via fecal route Rosiglitazone: • Extensively metabolized to weakly active compounds primarily via CYP2C8 with minor pathway 2C9 • Excreted as metabolites in urine
Suitability for use in renal insufficiency	Caution if GFR 30-60 mL/min; Avoid if GFR < 30	Gliclazide & Glimepiride OK Glyburide – caution if GFR < 30	OK	OK

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Antihyperglycemic Agents Comparison Chart

Parameter	Metformin	Sulfonylureas	Meglitinides	Glitazones (TZD's)
Pharmacokinetic Drug Interactions Notes: (1) None of the antihyperglycemic agents is an important cause of drug interactions (no strong inhibitors or inducers). (2) Most of the pharmacokinetic data presented here describing alterations in the disposition of antihyperglycemic agents caused by inhibition or induction of metabolizing enzymes are of unknown clinical significance. Indeed, many are likely of no clinical significance based on the small magnitude of the effect. Exceptions include those for which it is recommended to "avoid" the combination and those for which an alteration in dosage of antihyperglycemic agent is recommended.	Cimetidine ↑ metformin AUC 50% (competitive inhibition of active renal tubular secretion)	**Sulfonylureas:** ↑ **AUC due to CYP2C9 inhibitor:** • Clarithromycin ↑ glyburide 35% • Fluconazole ↑ glimepiride 138% • Co-trimoxazole (TMP/SMX) ↓ clearance of tolbutamide 25% and ↑ half-life 30% ↓ **AUC due to CYP2C9 inducer:** • Rifampin ↓ gliclazide 70% • Rifampin ↓ glimepiride 34% • Rifampin ↓ glyburide 39%	**Repaglinide** ↑ **AUC due to CYP inhibitor:** • Clarithromycin 40% (3A4) • Cyclosporine 144% (3A4) • Gemfibrozil 712% (2C8 and OATP1B1); **avoid** combined use with repaglinide • Itraconazole 41% (3A4 and OATP1B1) • Itraconazole + gemfibrozil 1839% (20-fold increase) (2C8 & 3A4); **avoid** combined use of both drugs with repaglinide • Ketoconazole 15% (3A4) • Telithromycin 77% (3A4) • Trimethoprim 61% (2C8) ↓ **AUC due to CYP inducer:** • Rifampin 32-85% (3A4) **Nateglinide** ↑ **AUC due to CYP inhibitor:** • Fluconazole 48% (2C9) • Gemfibrozil + itraconazole 47% (2C8 & 3A4) ↓ **AUC due to CYP inducer:** • Rifampin 24% (2C9 & 3A4)	**Pioglitazone** ↑ **AUC due to CYP2C8 inhibitor:** • Gemfibrozil 230%; consider limiting dose of pioglitazone to 15 mg daily • Trimethoprim 42% ↓ **AUC due to CYP2C8 inducer:** • Rifampin 54% **Rosiglitazone** ↑ **AUC due to CYP inhibitor:** • Fluvoxamine 21% (2C8) • Gemfibrozil 130% (2C8); consider limiting dose of rosiglitazone to 4 mg daily • Ketoconazole 47% (3A4) • Trimethoprim 35% (2C8) ↓ **AUC due to CYP inducer:** • Rifampin 60% (2C8; also 2C9)
Products & Dosage Forms	• Metformin (Glucophage & generics) 500, 850 mg • Glumetza extended release (ER) 500, 1000 mg Combination products: • Avandamet – see Glitazones • Janumet – see DPP-4 Inhibitors	• Gliclazide (Diamicron & generics) 80 mg modified release (MR) 30 mg • Glimepiride (Amaryl & generics) 1 mg, 2 mg, 4 mg • Glyburide (Diabeta & generics) 2.5, 5 mg	• Repaglinide (Gluconorm & generics) 0.5 mg, 1 mg, 2 mg • Nateglinide (Starlix) 60, 120, 180 mg	• Pioglitazone (Actos & generics) 15, 30, 45 mg • Rosiglitazone (Avandia) 2, 4, 8 mg • Avandamet = Rosiglitazone + Metformin 1/500 mg, 2/500 mg, 4/500 mg, 2/1000 mg, 4/1000 mg

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Antihyperglycemic Agents Comparison Chart

Parameter	Metformin	Sulfonylureas	Meglitinides	Glitazones (TZD's)
Dosage	***To improve GI tolerability, start with a low dose and increase slowly every 3-5 days*** • Metformin is taken 2-3 times per day with or after meals; Start with 500 once or twice daily; increase by 500 mg/day as tolerated; max 2.5 g /day • Glumetza is taken once daily with evening meal; start with 1 g and increase by 500 mg at weekly intervals; max 2 g/day	***Most of the benefit of a sulfonylurea is achieved in most patients at half the max daily dose listed below*** • Gliclazide is taken twice daily before breakfast & supper; start with 80 mg BID; max 160 mg BID • Glimepiride is taken once daily before breakfast; start with 1 mg daily; increase every 1-2 weeks; max 8 mg daily • Glyburide is taken once daily or twice daily if the dose/day exceeds 10 mg; start with 2.5 to 5 mg daily; increase every 1-2 weeks; max 20 mg/day	***Meglitinides are to be taken within 30 min prior to a meal and only if patient will be eating.*** ***If a meal is delayed or will not be eaten, the dose should usually be delayed or omitted.*** • Repaglinide: start with 0.5 to 1 mg TID; max 12 mg/day • Nateglinide: start with 120 mg TID; max 540 mg/day	***Before increasing dose, allow 8-12 weeks to assess full benefit*** • Pioglitazone is taken once daily without regard to mealtimes; start with 15 or 30 mg daily; max 45 mg/day • Rosiglitazone is taken once daily without regard to mealtimes; start with 4 mg daily; max 8 mg/day
Cost per month for most common dose < $15 $ $16-35 $$ $36-70 $$$ $71-100 $$$$ > $100 $$$$$	Metformin $ Glumetza $$$	Gliclazide $ Gliclazide MR $ Glimepiride $$ Glyburide $	Repaglinide $$ Nateglinide $$$	Pioglitazone $$$ Rosiglitazone $$$$ Avandamet $$$$ to $$$$$
Coverage by public drug plan (ODB)	Metformin YES Glumetza NO	Gliclazide YES Glyburide YES Glimepiride NO	NO	NO
Advantages	• Efficacy (major A1c reduction) • More durable glycemic control than sulfonylurea • No hypoglycemia • No weight gain; possible modest weight loss • Possible CV benefit • Best oral agent for use with insulin (less weight gain; lower insulin dose) • Low cost generics • ODB coverage	• Efficacy (major A1c reduction) • Well tolerated • OK in renal insufficiency (caution: glyburide) • Once-daily dosing possible • Low cost generics • ODB coverage for some (glyburide & gliclazide)	• Efficacy: A1c reduction with Repaglinide is similar to sulfonylureas (but less with Nateglinide) • Less hypoglycemia than sulfonylureas (especially in patients who may miss meals) • Well tolerated • OK in renal insufficiency	• Efficacy (major A1C reduction) • More durable glycemic control than sulfonylurea • No hypoglycemia • OK in renal insufficiency • Well tolerated • Once-daily dosing

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Antihyperglycemic Agents Comparison Chart

Parameter	Metformin	Sulfonylureas	Meglitinides	Glitazones (TZD's)
Disadvantages or Factors Limiting Use	• Dose-related GI intolerance initially (5-20%) • Malabsorption of vitamin B12 may result in anemia • Many precautions or contraindications (risk factors for lactic acidosis) - Renal impairment - Hepatic disease - Alcoholism - Severe heart failure - Severe respiratory disease	• Hypoglycemia • Risk ranking highest to lowest: glyburide > glimepiride > gliclazide • Weight gain • Efficacy declines over time more than metformin or glitazones	• Compliance may be a challenge (TID ac dosing) • Nateglinide A1C ↓ modest • Higher cost than sulfonylureas • No ODB coverage	• Slow onset of maximal glucose-lowering effect (8-12 wks) • Many precautions or contraindications: - Fluid retention, edema - Risk of new or worsened heart failure is double that of other agents - Contraindicated in any stage of heart failure - Weight gain can be significant - Fracture risk is doubled - Rosiglitazone may increase risk of myocardial infarction by 30-40% - Pioglitazone doubles risk of bladder cancer • Moderately expensive • No ODB coverage
Place in Therapy	• Drug of choice for all patients as monotherapy or combination therapy, especially insulin-requiring patients	• Second line therapy, for addition to metformin or for initial use when metformin is not an option	• Useful in patients who require an insulin secretagogue but who are at risk of sulfonylurea-induced hypoglycemia (especially that which may be due to an irregular meal schedule)	• Glitazones are less commonly used now (DPP-4 inhibitors have become preferred third-line agents, particularly since coverage by public drug plan [ODB] was introduced) • Pioglitazone is the preferred agent in class • Rosiglitazone is rarely used, and only if all other therapies are deemed to be unsuitable

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Antihyperglycemic Agents Comparison Chart

Parameter	DPP-4 Inhibitors	GLP-1 Agonists	Insulin	Acarbose
Mechanism of Action	Enhance incretin activity ↑ Insulin secretion (primarily prandial) ↓ Glucagon secretion These actions occur only when blood glucose levels are elevated; they do not cause hypoglycaemia or impair ability to recover from hypoglycemia	Enhance incretin activity ↑ Insulin secretion (primarily prandial) ↓ Glucagon secretion These actions occur only when blood glucose levels are elevated; they do not cause hypoglycaemia or impair ability to recover from hypoglycemia	Corrects insulin deficiency ↑ Peripheral glucose uptake ↓ Hepatic glucose output	Alpha-glucosidase inhibitor Slows digestion of carbohydrate, thereby slowing postprandial glucose absorption
Efficacy (A1C Reduction)	0.5 - 1%	Exenatide 0.5 – 1.0% Liraglutide 0.8 – 1.5%	Variable (1.5 – 3.5 %)	0.5 – 1%
Hypoglycemia	0	0	+++++	0
Weight Change	0	↓↓ (dose-related)	↑↑↑ (dose-related)	0
Suitability in heart failure	OK	OK	OK (Caution: ↑ risk of HF if used in combination with a glitazone)	OK

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Antihyperglycemic Agents Comparison Chart

Parameter	DPP-4 Inhibitors	GLP-1 Agonists	Insulin	Acarbose
Metabolism & Excretion	**Linagliptin:** • Minimal metabolism • Excreted primarily as unchanged drug (85%) via fecal route **Saxagliptin:** • Extensively metabolized via CYP3A4/5 (1 active metabolite) • Excreted primarily as inactive metabolites; 24% as unchanged drug; 26% as active metabolite **Sitagliptin:** • Minor metabolism via CYP3A4 & 2C8 to inactive compounds • Excreted primarily as unchanged drug in urine (80%) **Alopgliptin:** • Minimal metabolism • Excreted primarily as unchanged drug in urine (95%) **Vildagliptin:** • Extensively metabolized (55%) to inactive compounds via non-CYP hydrolysis • Excreted primarily as inactive metabolites (21-33% as unchanged drug)	**Exenatide:** • Minimal metabolism • Excreted renally unchanged **Liraglutide:** • Extensively metabolized to inactive compounds by endogenous endopeptidases • Excreted as inactive metabolites	Exogenous insulin is cleared primarily by the kidneys	Acarbose is metabolized to inactive compounds in GI tract and < 2% reaches systemic circulation
Suitability for use in renal insufficiency (Health Canada approvals)	• Linagliptin not renally excreted; but still "not recommended" if GFR < 30 (based on a lack of experience in these patients) • Saxagliptin approved at 2.5 mg daily for GFR 10-50 mL/min • Sitagtliptin ""not recommended" if GFR < 50 (based on a lack of experience in these patients) • Janumet: see metformin	• Exenatide contraindicated if GFR < 30; caution if GFR 30-50 • Liraglutide "not recommended" if GFR < 50 (based on a lack of experience in these patients)	OK	OK

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Antihyperglycemic Agents Comparison Chart

Parameter	DPP-4 Inhibitors	GLP-1 Agonists	Insulin	Acarbose
Pharmacokinetic Drug Interactions Note: most of the pharmacokinetic data presented here describing alterations in the disposition of antihyperglycemic agents caused by inhibition or induction of metabolizing enzymes are of unknown clinical significance. Indeed, many are likely of no clinical significance based on the small magnitude of the effect. Exceptions include those for which it is recommended to "avoid" the combination and those for which an alteration in dosage of antihyperglycemic agent is recommended.	**Saxagliptin** ↑ **AUC due to CYP3A4 inhibitor:** • Diltiazem 109% • Ketoconazole 145%; consider reducing dose of saxagliptin by 50% (to 2.5 mg daily) ↓ **AUC due to CYP3A4 inducer:** • Rifampin 76% **Linagliptin** No significant metabolic drug interactions **Sitagliptin** No significant metabolic interactions **Alogliptin** No metabolic drug interactions **Vildagliptin** No metabolic drug interactions	No known pharmacokinetic drug interactions	No known pharmacokinetic drug interactions	Digestive enzyme products containing amylase may reduce the effect of acarbose; avoid concomitant administration (H)
Products & Dosage Forms	• Linagliptin (Trajenta) 5 mg • Saxagliptin (Onglyza) 2.5, 5 mg • Sitagliptin (Januvia) 100 mg • Janumet (sitagliptin 50 mg + metformin 500, 850, or 1000 mg)	• Exenatide (Byetta) 1.2 mL or 2.4 mL prefilled disposable pens • Liraglutide (Victoza) 18 mg per 3 mL prefilled disposable pen	• Rapid-acting analogues (aspart, glulisine, lispro) • Short-acting insulin ("regular insulin") • Intermediate-acting insulin (NPH insulin) • Long-acting analogues (detemir, glargine)	Acarbose (Glucobay) 50, 100 mg

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Antihyperglycemic Agents Comparison Chart

Parameter	DPP-4 Inhibitors	GLP-1 Agonists	Insulin	Acarbose
Dosage	***DPP-4 inhibitors are taken once daily without regard to mealtimes*** • Linagliptin 5 mg once daily • Saxagliptin 5 mg once daily or 2.5 mg once daily if GFR 10-15 mL/min • Sitagliptin 100 mg once daily • Janumet (sitagliptin + metformin) is taken BID with or after meals	***GLP-1 agonists must be injected subcutaneously.*** • Exenatide is injected twice daily 0-60 min before breakfast & supper. Start with 5 mcg SC BID for first month; if tolerated, may increase to 10 mg SC BID • Liraglutide is injected once daily without regard to mealtimes. Start with 0.6 mg SC once daily for at least first week; if tolerated, increase to 1.2 mg SC once daily; max 1.8 mg/day	Variable	• Acarbose must be taken with the first bite of a meal (if taken after meal, efficacy is significantly reduced). If no meal is to be eaten, dose should be omitted. • To improve GI tolerability, start with a low dose and increase slowly every 3-5 days • Start with 25 mg 1-2 times/day; increase dose by 25-50 mg/day if tolerated every 3-5 days; usual max 150 mg/day (higher doses are poorly tolerated)
Cost per month for most common dose < $15 $ $16-30 $$ $31-70 $$$ $71-100 $$$$ > $100 $$$$$	$$$$	$$$$$	**Varies by product & dosage** Initial basal insulin regimen: • NPH daily at bedtime (50 units) $$$ • Detemir or Glargine once daily (50 units) $$$$	$$
Coverage by oublic drug plan (ODB)	Linagliptin NO Saxagliptin YES Sitagliptin YES Janumet YES	NO	YES	YES
Advantages	• No hypoglycemia • No weight gain (neutral effect) • Well tolerated • Fewer safety concerns than with the glitazones • Once daily dosing “anytime” and no dosage titration required • ODB coverage (most products)	• Efficacy: A1c reduction with Liraglutide may be similar to metformin, sulfonylureas, glitazones (greater than DPP-4 inhibitors and exenatide) • No hypoglycemia • Dose-related weight loss	• Greatest potential A1c reduction • Uniquely effective when oral agents prove inadequate • Consistently effective (lower failure rate) • Prompt improvement in blood glucose • Well tolerated • Cost of therapy can be reasonable (if regimen is simple and/or human insulin is used) • ODB coverage	• No hypoglycemia • Weight neutral • No systemic toxicity (negligible absorption) • OK in renal insufficiency

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Antihyperglycemic Agents Comparison Chart

Parameter	DPP-4 Inhibitors	GLP-1 Agonists	Insulin	Acarbose
Disadvantages or Factors Limiting Use	• A1C ↓ somewhat less than metformin, sulfonylureas, and glitazones • Long-term efficacy and safety unknown • Pancreatitis: avoid use of DPP-4 inhibitors in patients with risk factors: very high triglycerides; alcoholism; history of pancreatitis • Expensive	• Long-term efficacy unknown • Long-term safety unknown (thyroid cancer?) • Pancreatitis: avoid use of GLP-1 agonists in patients with risk factors: very high triglycerides; alcoholism; history of pancreatitis • Renal insufficiency: exenatide is contraindicated if GFR < 30; caution for both agents if GFR < 50 • Must be injected (not attractive to patients with aversion to needle) • Major dose-related GI intolerance (30-50%) primarily during initial month • Most expensive drug class • No ODB coverage	• Hypoglycemia • Weight gain (dose-related) • Self-monitoring of blood glucose is a requirement • Dosage adjustments are usually required • Vision and dexterity problems may limit use • Low acceptance among many patients and perhaps also health care providers • Can be expensive (intensive regimens using analogues)	• A1C ↓ modest • Major dose-related GI intolerance (10-35%), particularly initially, requiring slow upward dosage titration • Compliance may be a challenge (must be taken with first bite of meals)
Place in Therapy	• Third-line agents for addition in patients not controlled on metformin + a secretagogue • Alternative to basal insulin when hypoglycemia and/or weight gain are concerns or patient refuses insulin injections	• Role not yet well established • May be considered for patients in whom weight loss is a primary goal and avoidance of hypoglycaemia is important	Type 2 diabetes: • Usually added when patients fail to achieve target A1c despite use of 2-3 agents • Also used temporarily in patients with severe metabolic stress (trauma, surgery, infection, MI)	• Limited role as an alternative when other agents are deemed unsuitable • Most useful when A1c is near target, and/or main problem is postprandial hyperglycemia

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