

APPROACH TO MANAGEMENT OF TYPE 2 DIABETES

Nonpharmacologic Therapy

♦ **Lifestyle Modifications** ¹ & **Patient Education** are important at all levels!!! ^{2,3,4}

If individualized goals for glucose are not achieved in 2-4 months,
 ⇒ reassess; advance to next level of therapy

See Health Canada's
 Food & Fitness Guides

Oral Hypoglycemic Monotherapy

♦ **If obese (BMI ≥30)**

⇒ start **metformin (MF) 500mg po OD or BID**
 (↑dose over 3-4 weeks; usual ≤2,000mg/day; lower doses in elderly-see Table 6)
 ⇒ alternative agents used if metformin contraindicated/not tolerated
 (e.g. acarbose, sulfonylureas, repaglinide, "glitazones"; see chart)

MF target dose in UKPDS (age ≤65):
 1700mg am + 850mg @supper (↓ mortality)

♦ **If non-obese**

⇒ start sulfonylurea (SU) or metformin (↑dose over 3-4 weeks)
 ⇒ consider acarbose or repaglinide if main target is **PPBG**
 ⇒ alternative agents such as "glitazones" may also be considered (note these agents can take a long time before effect seen (8-16 weeks). There are theoretical advantages to early use, but await studies on morbidity and mortality outcomes
 Repeat A1C; Reassess lifestyle modifications in 2-4 months,
 ⇒ If targets for glucose control not achieved, advance combination therapy
 (Combination therapy will be required in most Type 2 patients)

Oral Combination Therapy (2 agents often needed: after 3yrs 50%; after 9yrs 75%)

♦ a variety of 2-drug combinations may be considered esp. if A1C ≥9% initially (see Table 7)
 ♦ combination of repaglinide and sulfonylureas not usually recommended
 Repeat A1C; Reassess lifestyle modifications in 2-4 months,
 ⇒ If targets for glucose control not achieved, advance to next level of therapy

Add Insulin Therapy +/- Oral Agents

♦ **Option 1: Bedtime insulin** (e.g. Humalin N/Novolin N) + **daytime oral hypoglycemics**

⇒ if on SU + other oral agent, may consider discontinuing / reducing the SU
 - add intermediate acting insulin, 5-15units at HS (initial ~0.1units/kg; max 0.25units/kg)
 - ↑ insulin dose by 2 units every 3-4 days until fasting glucose of 4-7
 - may result in better control, lower insulin dose, less weight gain than insulin alone
 - if target BG not achieved at 30units/day, or if daytime BG rises, may switch to split-mixed insulin or a more intensive regimen (usual range: 0.25-1unit/kg/d)

♦ **Option 2: Switch to insulin therapy 1-4x/day**

⇒ may discontinue certain oral hypoglycemics (see Table 7)
 - adjust insulin dose and frequency to achieve target levels

e.g. **Split-mixed insulin regimen**

- estimate total starting daily dose (0.3-0.6 units/kg)
 - divide daily dose: 2/3 in morning before breakfast; 1/3 in evening before supper
 - divide each dose: 2/3 intermediate-acting & 1/3 short-acting insulin (or 30/70 mix)

Some patients may eventually require very high doses of insulin due to insulin resistance (max 400U/day in UKPDS)

(Note: insulin temporarily indicated in any pt with metabolic decompensation, severe fasting hyperglycemia, or severe illness.)

GLUCOSE TARGETS	Canadian 2003	Target for most	Normal range	→consider achieving if can be done	Note: role for individualizing targets (ie. less aggressive in frail elderly ³¹ ; more aggressive in younger candidates).
A1C q3-6 mon (calibrate meter qyr)		≤ 7	≤ 6		
FPG (mmol/L)		4-7	4-6	safely without	
PPBG (mmol/L) 2hr post		5-10	5-8	hypoglycemia etc..	
BP ²⁰⁰⁴	Diabetes→130/80 if no proteinuria; 125/75 if proteinuria >1g/d.				
LIPID ²⁰⁰³	Diabetes→ LDL<2.5 Total Chol/HDL<4				
RENAL		Normal	Microalbuminuria	Macroalbuminuria	
Albuminuria		<30mg/day (<20ug/min)	30-300mg/day (20-200ug/min)	>300mg/day (>200ug/min)	
Albumin mg/Creatinine mmol Ratio		Male <2; Female <2.8	Male 2-20; Female 2.8-28	Male >20; Female >28	

BMI (kg/m ²)	WEIGHT (Kg; lbs)																			
	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130		
HEIGHT (Cm; inches)	150	59	20	22	24½	26½	29	31	33	35½	38	40	42	44½	46½	49	51	53	55½	58
	155	61	18½	21	23	25	27	29	31	33	35½	37½	39½	41½	43½	46	48	50	52	54
	160	63	17½	19½	21½	23½	25½	27	29	31	33	35	37	39	41	43	45	47	49	51
	165	65	16½	18½	20	22	24	26	27½	29½	31	33	35	36½	38½	40½	42	44	46	48
	170	67	15½	17	19	21	22½	24	26	27½	29½	31	33	34½	36	38	40	41½	43	45
	175	69	14½	16	18	19½	21	23	24½	26	28	29½	31	32½	34½	36	37½	39	41	42½
	180	71	14	15½	17	18½	20	21½	23	24½	26	28	29	31	32½	34	35½	37	38½	40
	185	73	13	14½	16	17½	19	20½	22	23½	25	26	28	29	30½	32	33½	35	36½	38
	190	75	12½	14	15	16½	18	19½	21	22	23½	25	26	27½	29	30½	32	33	34½	36
	195	77	12	13	14½	16	17	18½	19½	21	22½	23½	25	26	27½	29	30	31½	33	34

Underweight = <18.5kg/m²; Normal = 18.5-24.9kg/m²; Overweight = 25-29.9kg/m²; Obese = ≥30kg/m²

Table 6: Individualization of Drug Therapy: Special Considerations

Patient Factor	Consider ⇒ possibly preferred drugs
Renal failure *	"Glitazones", repaglinide; also tolbutamide or gliclazide ⁵ , insulin
Hepatic disease	Insulin, repaglinide, acarbose (Caution: glyburide, metformin & glitazones)
Hypoglycemia	Metformin, "Glitazones", Acarbose; also repaglinide, nateglinide, gliclazide & glimepiride; insulin glargine
Obese	Metformin; Acarbose; also "Glitazones"
Irregular mealtimes	Repaglinide (may be preferred over SU)
PPBG >10mmol/l & FPG minimally ↑'d	Repaglinide or Acarbose Insulin lispro HUMALOG (if PPBG very high)

* Metformin dosing in elderly: lactic acidosis assoc. with metformin is rare (<1:10,000 treated pts)^{6,7,8}

Maximum Metformin Dose⁹: For CrCl 60 ml/min → 1700mg/d; 30 ml/min → 850mg/d; <30 ml/min → contraindicated

Table 7: Combination Therapy/Insulin Therapy in Type 2 Diabetes^{10,11}

Drug combination	↓ in A1C	hypo-glyc.	Wt	Comments (long-term outcomes not well studied!)
SU + MF	↓↓↓	↑↑	↑	♦if SU initial agent, may add MF or a TZD; (SU+MF may ↓A1C by additional 1.7%; one study found ↑mortality with combination ¹²) ♦if MF initial agent, may add SU or repaglinide ♦MF combos generally result in less weight gain than SU combinations; ♦MF+pioglitazone had positive lipid effects; ♦MF+acarbose: ↓ weight / PPBG but ↑GI SEs; ♦for hypoglyc. on acarbose: must treat with glucose as sucrose not absorbed
SU + TZD ¹³	↓↓	↑↑	↑↑	
SU + acarbose	↓	↑↑	↑	
MF+ repaglinide ¹⁴	↓↓	↑	↑	
MF+ TZD ^{15,16}	↓↓	↑	↑	
MF+ acarbose ¹⁷	↓	-	↓	
TZD + acarbose	↓	↑	↑	
Insulin monotherapy	↓↓↓	↑↑↑	↑↑↑	♦tight BG control but hypoglycemia/weight gain
Insulin + SU	↓↓↓	↑↑	↑↑	♦may improve glycemic control over insulin alone; caution in elderly due to hypoglycemia
Insulin + MF (FINFAT STUDY ¹⁸)	↓↓↓	↑	↑	♦overcomes insulin resistance; MF has positive effect on wt & lipids; preferred in obese patient; superior to insulin+SU; insulin sparing ~20-25%
Insulin+ pioglitazone or rosiglitazone*	↓↓ ¹⁹	↑↑↑	↑↑↑	♦overcomes insulin resistance; effective but more study needed (e.g. ↑ risk of edema/HF ²⁰)
Insulin+ repaglinide	↓↓	↑↑	↑↑	♦option to ↓ PPBG
Insulin + acarbose	↓	↑↑↑	↑↑↑	♦recommended to ↓ PPBG when diet high in CHOs; may also ↓ weight & triglycerides

♦some 3-drug regimens useful for glycemic control but not well studied (e.g. Insulin+SU+MF)







A1C = glycosylated hemoglobin BG= blood glucose CHO= carbohydrate FPG= fasting plasma glucose HF= heart failure MF= metformin PPBG = postprandial blood glucose SE= side effects SU= sulfonylurea TZD= pioglitazone & rosiglitazone Wt= weight *official labeling: "not indicated"

Oral HYPOGLYCEMIC AGENTS (OHA) - Comparison Chart


21-22-23-24-25-26-27-28-29-30-31-32,33,34

Prepared by: Loren Regier, Sharon Downey, Brent Jensen—www.RxFiles.ca

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Generic/TRADE/ (Strength) Pregnancy	KINETICS	EFFECTS ON							DRUG INTERACTION	COMMENTS	INITIAL & USUAL DOSE (Max.) DOSE	USUAL DOSE RANGE	\$  /100 day
		FPG	PPBG	A1C	LDL	HDL	TGs	Wt					
SULFONYLUREAS (SU) Insulin Secretagogue – stimulate insulin release from β cell; ↑ peripheral glucose utilization (↑ #/sensitivity of insulin receptors?); reduce hepatic gluconeogenesis													
Chlorpropamide DIABINESE , generic (100, 250mg scored tabs)	P = 6-8h D = 24-72h	↓	↓	↓	↓	↓	↓	↓	Numerous: • ↑ Hypoglycemic effect with: EtOH, NSAIDs, salicylates, sulfonamides, MAOIs, cimetidine. • β-Blockers may mask hypoglycemia • Disulfiram rx. with EtOH, mostly with chlorpropamide • rifampin ↓ effect	Does not correct impaired 1st phase insulin response; many (~75%) require 2 nd agent for adequate control (e.g. + metformin or TZD); ~1 st choice option for lean patient Hypoglycemia: most with chlorpropamide & glyburide (see note below); least: tolbutamide, glimepiride ^{35,36} & gliclazide ³⁷ Caution in elderly (hypoglycemia risk) & obese (wt gain). Require consistent food intake to avoid problems with hypoglycemia (↑ risk: elderly, debilitated, malnourished) SE: Wt gain , headache, dizziness, sulfa skin reactions (rash/photosensitivity ~1%), GI side effects ^{1-3%} ; concerns with cardiac toxicity & hyperinsulinemia. & hyponatremia Reduce dose if hypoglycemia or renal/hepatic dysfx Dose titration q1-2 weeks. Failure rates ~5-10%/year. In general, agents achieve ~75% of effect at 1/2 their max dose.	100mg od (500mg od)	100mg po od 250mg po od	 16  13
Gliclazide , generic DIAMICRON 80 ^{mg} tab. DIAMICRON MR 30 ^{mg} tab	P = 4-6h D = 10-24h	↓	↓	↓ 1-1.5	-	-	-	↑↑			40mg (160mg bid) 30mg (120mg od)	80mg po bid 60mg MR po od	72 89
Glyburide DIABETA , generic (2.5, 5mg scored tabs)	O = 15-60min P = 2-4h D = 12-24h	↓	↓	↓	-	-	-	↑↑			1.25-2.5mg od (10mg bid \$33)	5mg po od 5mg po bid 7.5mg po bid	 15  20  26
Tolbutamide , generic ORINASE (500mg scored tab)	P = 3h D = 6-12h	↓	↓	↓ 1-1.5	↓	↑	↓	-/↓	• EtOH and cimetidine ↑ effect • contrast media (long-term ↓ B ₁₂ & folate absorption) { Caution if CrCl ≤ 60ml/min }	Does not by itself cause hypoglycemia Possible wt loss vs wt gain; → DOC for OBES! SE: To avoid GI SEs, start low & titrate up q2-4wk Anemia 6-8:100 (due to B12 malabsorption) Avoid if severe renal dysfx/CHF or hepatic disease (lactic acidosis 1:10,000) ⁷ . +SU, TZD, Ins., CMBA Elderly: dose reduction required. ³⁹ May prevent NIDDM ⁴⁰ DPP	250mg od (1000mg tid)	500mg po bid 500mg po tid	27 37
Glimepiride AMARYL X ⊗ (1,2,4mg scored tab)	1mg od (\$90); 2mg od (\$90); 4mg od (\$90) /100days	↓	↓	↓ 1-1.5	↓	↑	↓	-/↓			1700mg po am, 850mg po pm: UKPDS TID dosing option for larger doses to ↓ GI intolerance (dyspepsia, nausea & diarrhea)	22 42 35 59	
BIGUANIDES – increase insulin sensitivity and cellular glucose uptake & utilization; reduce hepatic glucose production; ↓ morbidity & mortality in obese patients (UKPDS-34)													
Metformin ³⁸ (MF) GLUCOPHAGE , generic (500 ^c , 850mg tab)	P = 3h D = 8-12h	↓	↓	↓ 1-1.5	↓	↑	↓	-/↓	• +ve effect on lipids & weight	Does not by itself cause hypoglycemia Possible wt loss vs wt gain; → DOC for OBES! SE: To avoid GI SEs, start low & titrate up q2-4wk Anemia 6-8:100 (due to B12 malabsorption) Avoid if severe renal dysfx/CHF or hepatic disease (lactic acidosis 1:10,000) ⁷ . +SU, TZD, Ins., CMBA Elderly: dose reduction required. ³⁹ May prevent NIDDM ⁴⁰ DPP	250-500mg od (850mg tid)	500mg po bid 850mg bid 1g po bid	22 42 35 59
Metformin/Rosiglitazone AVANDAMET ⊗ ⊗ tabs (500mg/1,2,4mg BID = \$150, \$260, \$350 /100day tab; 1gm/2,4mg = \$280, \$380)		↓	↓	↓ 1-1.5	↓	↑	↓	-/↓			1700mg po am, 850mg po pm: UKPDS TID dosing option for larger doses to ↓ GI intolerance (dyspepsia, nausea & diarrhea)	22 42 35 59	
α GLUCOSIDASE INHIBITORS –inhibit α-glucosidases in brush border of small intestine; prevent hydrolysis & delay carbohydrate digestion (Tx hypoglycemia with glucose/Insta-gluc, honey or milk)													
Acarbose PRANDASE (50,100mg scored tabs)	Meal-time dosing; may take several weeks for max. effect	↓	↓	↓	-	-	-/↓	-/↓	• ↓ digoxin effect • Cholestyramine & cathartics ↑ effect • amylase & pancreatic enzymes ↓ effect • ↓ Fe ⁺⁺ ? (sucrose not absorbed)	Does not by itself cause hypoglycemia ↑ Liver enzymes = 3% with acarbose; monitor. (Caution as may accumulate in chronic renal failure.) SE: GI intolerance: flatulence >41%, diarrhea >28%. Maximal effect takes weeks; ↑ dose q4-8wks ROLE: useful in pts with ↑ PPBG; + SU, MF; (+Ins.?)	25mg od (100mg tid) STOP-NIDDM ⁴¹	50mg po tid 100mg po tid	94 127
Miglitol (not yet available in Can.) GLYSET (25,50,100mg tab)		↓	↓	↓ .5-8	-	-	-/↓	-/↓			25mg od (100mg tid)	25mg po tid 50mg po tid	N/a N/a
THIAZOLIDINEDIONES (TZDs) or GLITAZONES –Insulin Sensitizers: ↓ hepatic output of glucose & ↑ peripheral insulin uptake; ~ 4+ weeks before effect (adjust dose at ~3 months)													
Pioglitazone ACTOS (15, 30, 45 mg tab)	Delayed action... Onset ~3wks	↓	↓	↓	-	↑	↓	-/↑	• Cholestyramine ↓ absorption ~70% • Hepatic CYP _{2C8} • rosigl. not CYP _{3A4} • ↓ effect of oral contraceptives? • rosigl. ↑ by gemfibrozil & ↓ by rifampin	More effective in obese or hyperinsulinemia patients Does not by itself cause hypoglycemia; resumption of ovulation in anovulatory premenopausal women SE: Edema 4.8% (HF^{42,43}.HTN); Wt gain; 1% mild anemia (due to hemodilution?); monitor liver fx (ALT) when indicated; pioglitazone may have more +ve lipid effect ^{44,45} ROLE: + MF,SU; (possibly alone or + Ins. but ↑ HF risk)	15mg od (45mg/day)	15mg po od 30mg po od 45mg po od	249 338 491
Rosiglitazone AVANDIA (2, 4, 8mg tab)	Max effect in 8-16 wks	↓	↓	↓ 1-1.5	46,47	48,49	-/↓	-/↑			4mg od (4mg bid) bid dose –more effective (50)	4mg po od 4mg po bid 8mg po od	246 465 340
CARBAMOYL BENZOIC ACID DERIVATIVES (CMBAs) – short-acting insulin secretagogue; bind to β cell to stimulate insulin release at different site than SUs; (adjust dose at ~7days)													
Nateglinide STARLIX (60, 120, 180mg tab)	O = <20min P = 60-120min D = ~4h	↓	↓	↓ .5	-	-	-	-/↑	• CYP inhibitors ↑ effect: azole-antifungals, erythromycin, gemfibrozil • CYP inducers ↓ effect: barbs, carbamaz & rifampin	Restores 1 st phase insulin release - (↓ PPBG) Rapid, short duration ⇒ ↓ risk of hypoglycemia vs SUs ∴ option in elderly; {Flexibility with food intake: skip dose if skip meal; take extra dose if add meal} If stop other hypoglycemics begin next day & watch for hypoglycemia. ROLE: alone or + MF, TZD, or insulin	60mg tid ac (180mg po tid)	60mg po tid 120mg po tid 180mg po tid	200
Repaglinide GLUCINORM (0.5, 1, 2mg tab)	O = 15-60min P = 60-90min D = ~4-6h	↓	↓	↓ 1-1.5	-	-	-	-/↑			0.5mg tid ac (if no prev tx or A1C <8%) (4mg qid)	0.5mg po tid 1-2mg po tid 4mg po tid	110 220

↓ = dose for renal dysfx ⚡ = scored tab \$ Cost = total cost & markup in Sask; ⚡ = Exception Drug Status in SK X = Non-formulary in SK ⚡ = prior approval for NIHB ⊗ = not covered by NIHB ▼ covered by NIHB; ‘+’ denotes combination options
 A1C = glycosylated Hemoglobin (reflects glycemic control over prior 8-10 weeks) BP= blood pressure DOC= drug of choice dysfx= dysfunction EtOH= alcohol FPG= fasting plasma glucose GI= gastrointestinal HDL= high density lipoprotein HF= heart failure Ins.= Insulin KINETICS: O= onset P= peak D= duration; LDL= low density lipoprotein PPBG= postprandial blood glucose SE= side effects Wt= weight ⚡ = scored tablet
Drug induced ↑ glucose: antipsychotics, corticosteroids, cyclosporine, diuretics (thiazides e.g. >25mg HCT), estrogens, interferon^{alpha}, nicotinic acid ↑ dose, phenytoin, sympathomimetics (decongestants), tacrolimus & thyroid meds.
 Beta-blockers minimal risk of altering glucose control but may alter/mask hypoglycemic response. **Pregnancy:** Encourage diet, moderate exercise; Avoid oral hypoglycemics; Add **insulin** as needed if FBG >5.5 & 2hr PPBG >7.⁵¹
Hypoglycemia risk -UKPDS: risk of ≥1 MAJOR hypoglycemic events/yr (ITT): chlorpropamide=1%, glyburide=1.4%, **insulin 1.8%**; risk of ANY hypoglycemic event/yr chlorprop. = 16%, glyburide=21%, insulin 28%.
Oral agents +/- insulin: with progression of Type 2 diabetic disease, combo therapy with oral agents &/or addition of insulin to the regimen may eventually be required.
PPBG may better reflect risk of cardiovascular disease & all-cause mortality than FBG⁵²; **FBG & A1C are greater predictors of microvascular complications.**
 • Consider: ⁵³ ASA ~81mg/d, control of lipids, diet/exercise, orlistat⁵⁴, ↓ hypertension ACE Inhibitor/ARB/thiazide & DC smoking!

New: not in  → Exenatide **BYETTA X ⊗ an incretin mimetic 5-10mcg SC bid ac, ↑ insulin secretion, may ↓wt & ↑nausea. Pramlintide **SYMLIN** X ⊗ an amylinomimetic, 15-60-120mcg SC tid ac may ↓wt & ↑nausea.**

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(CONCLUSIONS: Sibutramine, orlistat, phentermine, probably diethylpropion, bupropion, probably fluoxetine, and topiramate promote modest weight loss when given along with recommendations for diet. Sibutramine and orlistat are the 2 most-studied drugs.)
(InfoPOEMs: On the basis of flimsy evidence of benefit, The American College of Physicians recommends drug therapy for the treatment of obesity. They also recommend gastric bypass surgery, performed by an experienced surgeon, for patients with marked obesity and other risk factors for premature death. (LOE = 5))

Additional articles:

- Chanoine JP, Hampl S, Jensen C, et al. Effect of **orlistat** on weight and body composition in obese adolescents. A randomized controlled trial. JAMA 2005;293:2873-83. (InfoPOEMs: Orlistat (Xenical), in combination with diet, exercise, & behavioral modification, improves weight management in obese adolescents. No major safety issues were identified after 1 year, but further follow-up for sustained weight management and safety is important. (LOE = 1b))
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