

Treating Type 2 Diabetes in 2017: How Not to Get Lost in the Forest

**Adirondack Health Institute
2017 Summit
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1. Describe how to individualize a diabetes treatment plan based on clinical characteristics

2. Describe the mechanism of action of 3 classes of diabetes medications excluding insulin analogs.

3. Describe the use of insulin replacement therapy in combination with other antihyperglycemic medications.

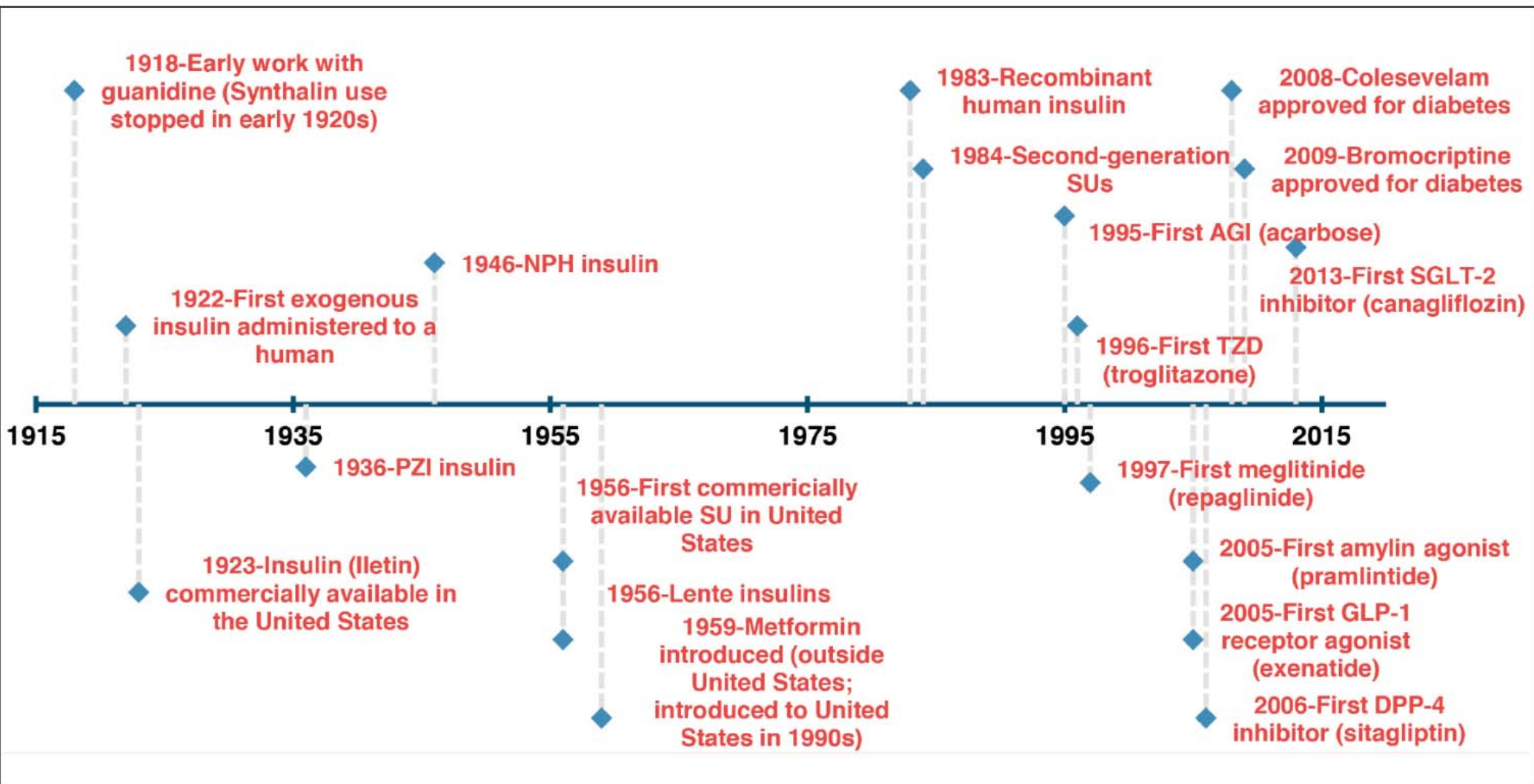
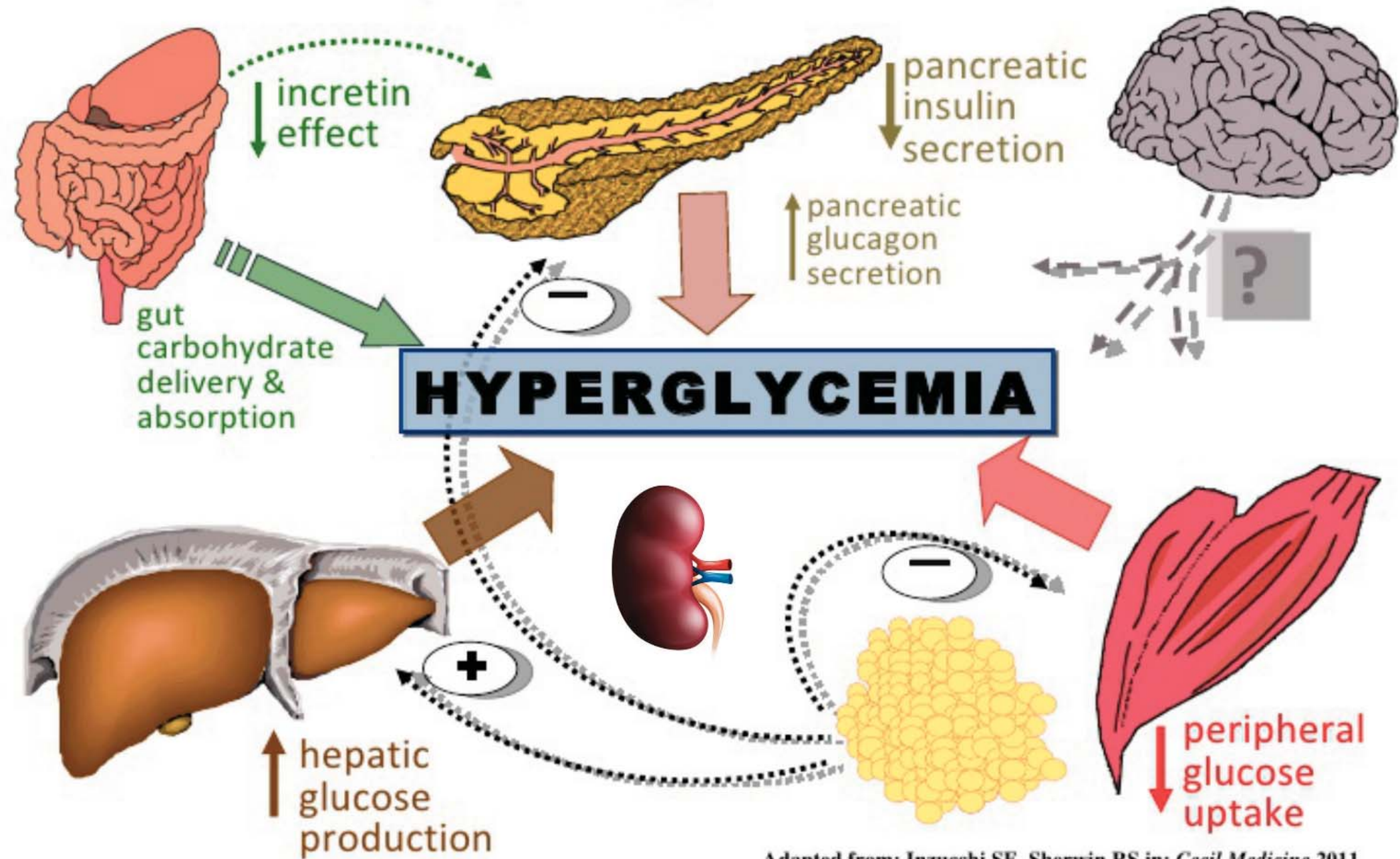


Figure 1. History of diabetes medications.

John R. White, Jr., PA-C, PharmD



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

50 yo man, 6'1", 255#, BMI 34

HTN, Gout, GERD

Since age 45: Random VBG 100-180
Diabetes?

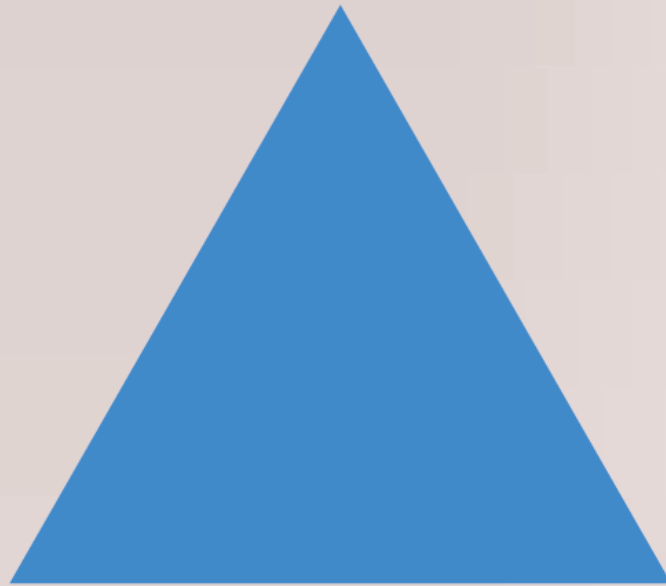
A1c 7.4%



48 yo man, 6'0", 176#, BMI 24
HTN, Tobacco abuse
A1c 7.4%



Diet



Exercise

Insulin

55 yo man, 6'1", 285#, BMI 38
HTN, Gout, GERD, DM2
Metformin

Hyperlipidemia, Fatty Liver
HbA1c 8.9%



Efficacy
Hypo Risk
Weight
Side Effects
Cost

Table 1. Advantages and Adverse Effects

Clinical

| Drug Class (A1C Reduction) ¹ | Some Advantages | Adverse Effects |
|---|---|---|
| Biguanide (1-1.5%) | | |
| Metformin | Durable A1C lowering; weight neutral or weight loss (2-3 kg); hypoglycemia is rare when used as monotherapy | Gastrointestinal effects (metallic taste, nausea, diarrhea, abdominal pain) ² ; vitamin B12 deficiency ³ ; cognitive decline ⁴ ; lactic acidosis ⁵ |
| Sulfonylureas⁶ (1-1.5%) | | |
| Glimepiride, Glipizide, Glyburide | Inexpensive; demonstrated long-term reduction in microvascular risk | Hypoglycemia; weight gain; possible aggravation of myocardial ischemia; glyburide has a higher incidence of hypoglycemia and mortality than glimepiride or glipizide ⁷ |
| Meglitinides (0.5-1%) | | |
| Nateglinide, Repaglinide | Short-acting | Hypoglycemia; weight gain; must be taken before each meal; use with caution in patients with moderate to severe liver disease; increased risk of hypoglycemia in patients with severe renal impairment taking nateglinide |
| Thiazolidinediones (1-1.5%) | | |
| Pioglitazone, Rosiglitazone | Low risk of hypoglycemia; durable A1C lowering | Weight gain (2-3 kg over 6-12 months) ⁸ ; peripheral edema; increased risk of heart failure ^{9,10} ; macular edema; decrease in bone mineral density and increased incidence of fractures, especially in women ¹¹ ; hepatic failure; pioglitazone has been associated with an increased risk of bladder cancer with high doses and long-term use ¹² |
| GLP-1 Receptor Agonists (1-1.5%) | | |
| Exenatide, Liraglutide | Weight loss ¹³ ; no hypoglycemia when used as monotherapy; <i>Bydureon</i> is administered once weekly | Nausea ¹⁴ ; vomiting; diarrhea; renal insufficiency and acute renal failure with nausea and vomiting ¹⁵ ; acute pancreatitis; can decrease the rate and extent of absorption of other drugs; should not be used in patients with gastroparesis; thyroid C-cell carcinomas have been reported in animals and thyroid C-cell hyperplasia has been reported in humans (liraglutide and extended-release exenatide) ¹⁶ ; must be injected subcutaneously |
| DPP-4 Inhibitors (0.5-1%) | | |
| Sitagliptin, Saxagliptin, Linagliptin, Alogliptin | Weight neutral; hypoglycemia is rare when used as monotherapy ¹⁷ | Hypersensitivity reactions (urticaria, angioedema, anaphylaxis, Stevens-Johnson syndrome, and vasculitis); acute pancreatitis; fatal hepatic failure; long-term safety unknown; higher rate of hospitalization for heart failure in one study with saxagliptin ¹⁸ |
| Alpha-Glucosidase Inhibitors (0.5-1%) | | |
| Acarbose, Miglitol | No hypoglycemia when used as monotherapy ¹⁹ | Abdominal pain, diarrhea, and flatulence ²⁰ ; contraindicated in patients with intestinal disease; acarbose can cause transaminase elevations |
| SGLT2 Inhibitors (0.5-1%) | | |
| Canagliflozin, Dapagliflozin | Weight loss; risk of hypoglycemia comparable to placebo ²¹ | Genital mycotic infections in men and women; recurrent urinary tract infections; volume depletion; increased urinary frequency and volume; increased serum creatinine and decreased eGFR; hyperkalemia; hypermagnesemia; hyperphosphatemia; fractures; increase in LDL-cholesterol; increased risk of cardiovascular events in the first 30 days of treatment; cardiovascular and long-term safety unknown; possible increased risk of bladder cancer with dapagliflozin |
| Others (0.5%) | | |
| Pramlintide | Weight loss | Nausea; vomiting; headache; anorexia; may delay or decrease absorption of other drugs; contraindicated in patients with gastroparesis or in those taking drugs that alter gastric motility; must be injected subcutaneously; severe hypoglycemia (when taken with insulin) |
| Colesevelam | No hypoglycemia | Constipation; nausea; dyspepsia; increases serum triglyceride concentrations; interferes with the absorption of other drugs |
| Bromocriptine | No hypoglycemia; may reduce risk of cardiovascular events | Nausea, vomiting, fatigue, headache, and dizziness (more common during titration and lasting for a median of 14 days); somnolence; orthostatic hypotension; syncope, especially in patients taking antihypertensives; lowers prolactin levels |

1. When used as monotherapy.

Table 2. Formulations, Dosage, and Cost (continued)

Cost-1

| Drug | Some Available Formulations | Pregnancy Category ¹ | Usual Daily Dosage | Cost ² |
|---|--|---------------------------------|--|-------------------|
| Alpha-Glucosidase Inhibitors | | | | |
| Acarbose – generic | 25, 50, 100 mg tabs | B | 50-100 mg PO tid ^{4,23} | \$ 44.60 |
| <i>Preco</i> se (Bayer) | | | | 88.20 |
| Miglitol – <i>Glyset</i> (Pfizer) | 25, 50, 100 mg tabs | B | 50-100 mg PO tid ^{4,23} | 138.60 |
| SGLT2 Inhibitors | | | | |
| Canagliflozin – <i>Invokana</i> (Janssen) | 100, 300 mg tabs | C | 100-300 mg PO once/d ^{7,24} | 289.10 |
| Dapagliflozin – <i>Farxiga</i> (BMS/AstraZeneca) | 5, 10 mg tabs | C | 5-10 mg PO once/d ²⁵ | 289.20 |
| Other | | | | |
| Colesevelam – <i>Welchol</i> (Daiichi Sankyo) | 625 mg tabs; 3.75g/packet | B | 3.75 g PO once or divided bid ⁴ | 334.80 |
| Bromocriptine ²⁶ – <i>Cycloset</i> (VeroScience) | 0.8 mg tabs | B | 1.6-4.8 mg PO once/d ²⁷ | 137.40 |
| Pramlintide – <i>Symlin</i> (AstraZeneca) | 1000 mcg/mL (1.5, 2.7 mL prefilled pen) | C | 60-120 mcg SC tid ²⁸ | 595.60 |
| Combination Products | | | | |
| Metformin/glipizide ³ – generic | 250/2.5, 500/2.5, 500/5 mg tabs | C | 500 mg/2.5 mg PO bid ⁴ | 45.80 |
| Metformin/glyburide ³ – generic | 250/1.25, 500/2.5, 500/5 mg tabs | B | 500 mg/5 mg PO bid ⁴ | 13.00 |
| <i>Glucovance</i> (BMS) | | | | 73.20 |
| Metformin/repaglinide ³ – <i>PrandiMet</i> (Novo Nordisk) | 500/1, 500/2 mg tabs | C | 500 mg/1-2 mg PO bid-tid ^{3,10} | 233.40 |
| Metformin/pioglitazone ³ – generic | 500/15, 850/15 mg tabs | C | 500 mg/15 mg PO bid ^{4,12} | 231.60 |
| <i>Actoplus Met</i> (Takeda) | | | | 393.00 |
| <i>Actoplus Met XR</i> | 1000/15, 1000/30 mg ER tabs | | 1000 mg/15 mg PO once ^{4,12} | 212.70 |
| Metformin/rosiglitazone ³ – <i>Avandamet</i> (GSK) | 500/2, 500/4, 1000/2, 1000/4 mg tabs | C | 500 mg/2 mg PO bid ^{4,13} | 137.80 |
| Metformin/alogliptin ³ – <i>Kazano</i> (Takeda) | 12.5/500, 12.5/1000 mg tabs | B | 12.5/500-12.5/1000 mg PO bid ⁴ | 283.90 |
| Metformin/linagliptin ³ – <i>Jentadueto</i> (Boehringer Ingelheim) | 500/2.5, 850/2.5, 1000/2.5 mg tabs | B | 1 tab PO bid ⁴ | 283.80 |
| Metformin/saxagliptin ³ – <i>Kombiglyze XR</i> (BMS) | 500/5, 1000/2.5, 1000/5 mg ER tabs | B | 1000-2000 mg/5 mg PO once/d ⁶ | 278.90 |
| Metformin/sitagliptin ³ – <i>Janumet</i> (Merck) | 500/50, 1000/50 mg tabs | B | 500 mg/50 mg PO bid ⁴ | 283.80 |
| <i>Janumet XR</i> | 500/50, 1000/50, 1000/100 mg ER tabs | B | 1000 mg/100 mg PO once/d ⁶ | 283.80 |
| Glimepiride/pioglitazone – <i>Duetact</i> (Takeda) | 2/30, 4/30 mg tabs | C | 4 mg/30 mg PO once/d ^{7,12} | 395.20 |
| Glimepiride/rosiglitazone – <i>Avandaryl</i> (GSK) | 1/4, 2/4, 4/4, 2/8, 4/8 mg tabs | C | 2 mg/4 mg PO bid ¹³ | 261.00 |
| Alogliptin/pioglitazone – <i>Oseni</i> (Takeda) | 12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, 25/45 mg tabs | C | 25/15-25/45 mg PO once/d ^{12,29} | 283.90 |

Table 2. Formulations, Dosage, and Cost

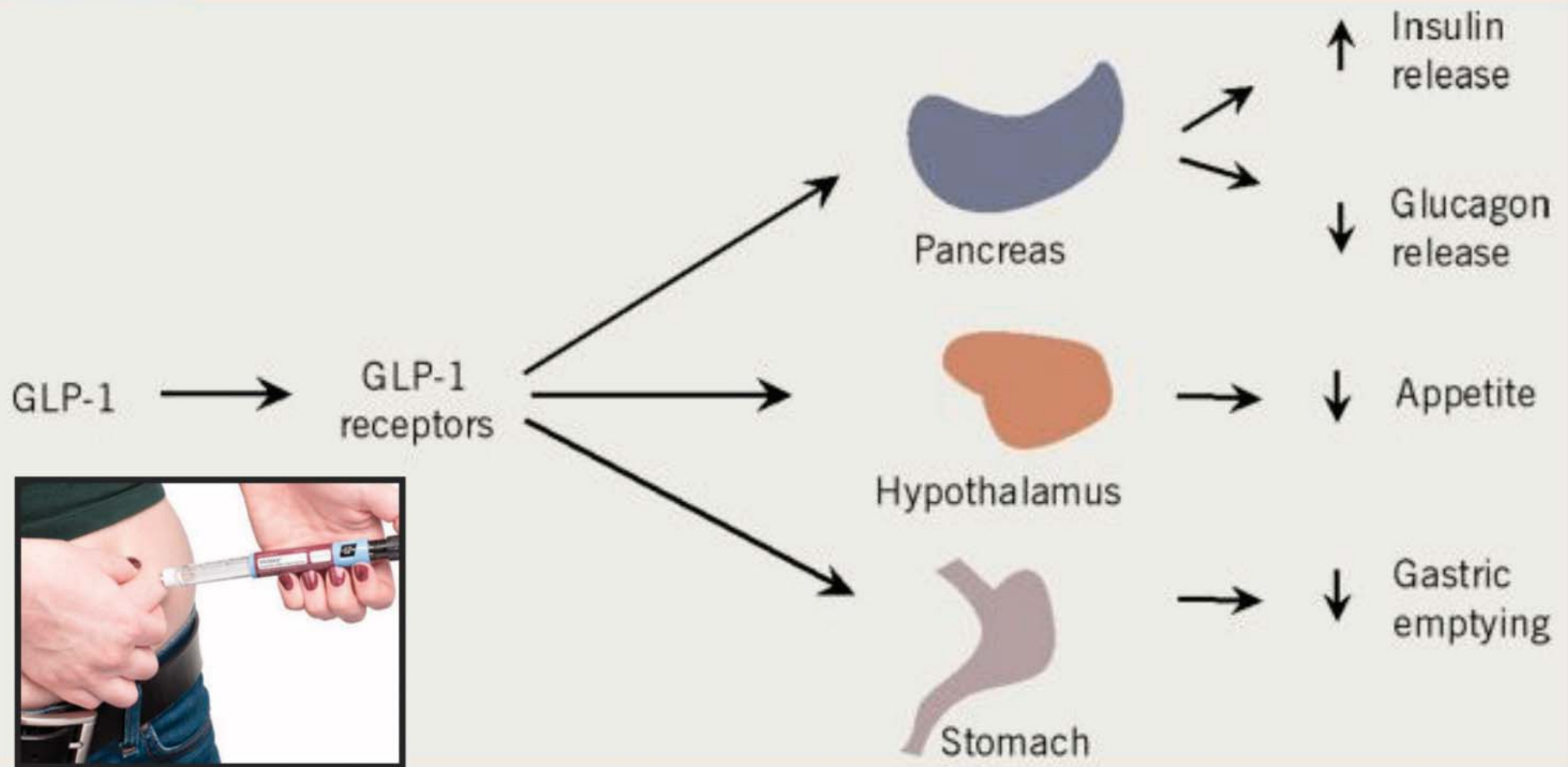
Cost-2

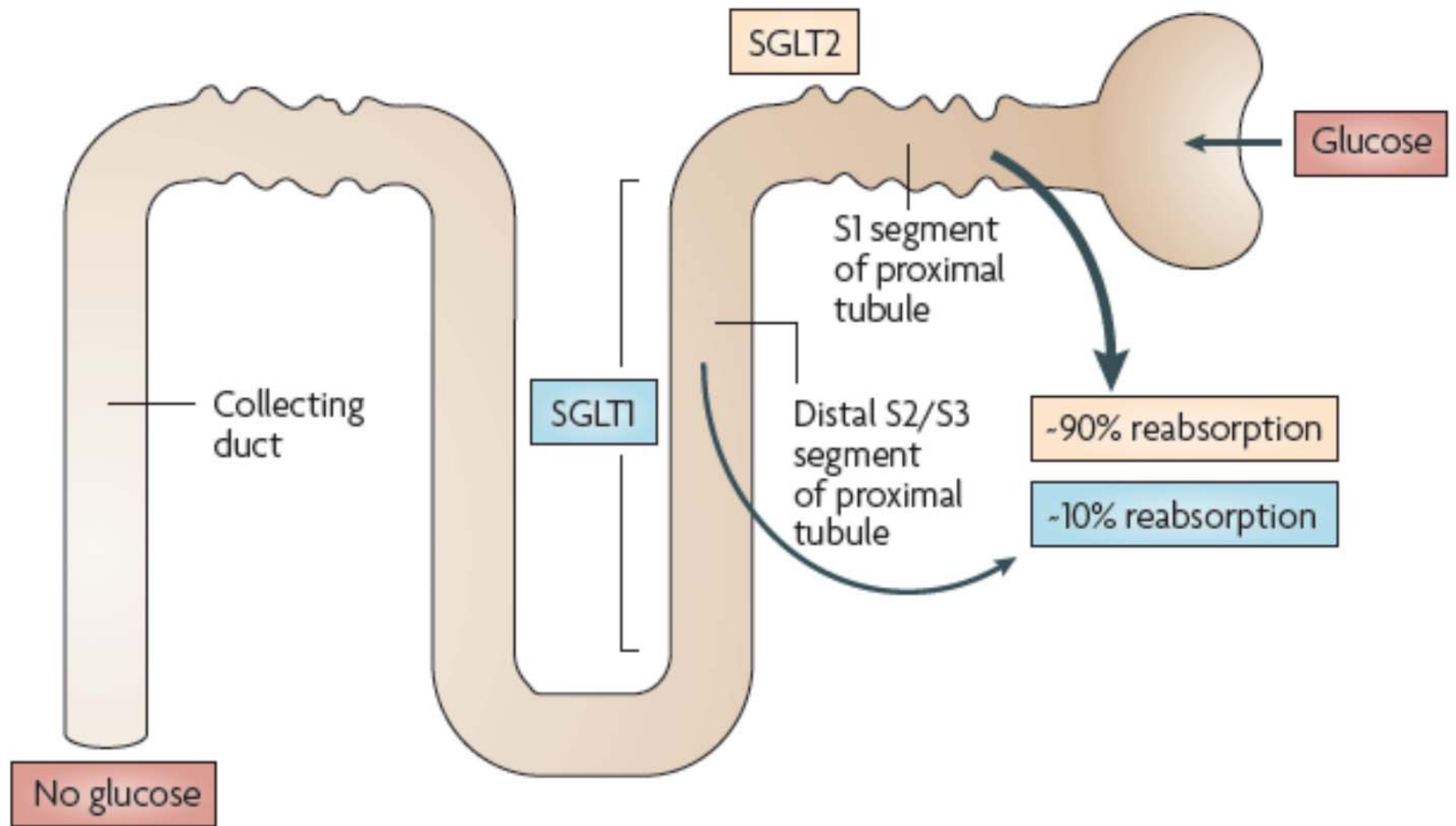
| Drug | Some Available Formulations | Pregnancy Category ¹ | Usual Daily Dosage | Cost ² |
|---|--|---------------------------------|---|----------------------|
| Biguanide | | | | |
| Metformin ³ – generic | 500, 850, 1000 mg tabs | B | 1500-2550 mg PO divided ⁴ | \$ 6.30 |
| <i>Glucophage</i> (BMS) | | | | 83.70 |
| liquid – <i>Riomet</i> (Ranbaxy) | 500 mg/5 mL (4, 16 oz) | | 1500-2550 mg PO divided ⁴ | 212.00 ⁵ |
| extended-release – generic | 500, 750 mg ER tabs | | 1500-2000 mg PO once/d ⁶ | 16.50 |
| <i>Glucophage XR</i> (BMS) | | | | 85.60 |
| <i>Glumetza</i> (Salix) | 500, 1000 mg ER tabs | | 500-2000 mg PO once/d ⁶ | 149.10 |
| <i>Fortamet</i> (Shionogi) | 500, 1000 mg ER tabs | | 1500-2500 mg PO once/d ⁶ | 1633.80 |
| Sulfonylureas | | | | |
| Glimepiride – generic | 1, 2, 4 mg tabs | C | 1-4 mg PO once/d ⁷ | 2.80 |
| <i>Amaryl</i> (Sanofi) | | | | 24.80 |
| Glipizide – generic | 5, 10 mg tabs | C | 10-20 mg PO once/d or divided ⁸ | 2.60 |
| <i>Glucotrol</i> (Pfizer) | | | | 47.10 |
| extended-release – generic | 2.5, 5, 10 mg tabs | | 5-20 mg PO once/d ⁷ | 10.10 |
| <i>Glucotrol XL</i> | | | | 25.20 |
| Glyburide ⁹ – generic | 1.25, 2.5, 5 mg tabs | C | 5-20 mg PO once/d or divided ⁷ | 9.60 |
| <i>DiaBeta</i> (Sanofi) | | | | 49.70 |
| micronized tablets – generic | 1.5, 3, 4.5, 6 mg tabs | B | 0.75-12 mg PO once/d or divided ⁷ | 1.60 |
| <i>Glynase Prestab</i> (Pfizer) | 1.5, 3, 6 mg tabs | | | 13.70 |
| Meglitinides | | | | |
| Nateglinide – generic | 60, 120 mg tabs | C | 60-120 mg PO tid ¹⁰ | 118.60 |
| <i>Starlix</i> (Novartis) | | | | 213.20 |
| Repaglinide – generic | 0.5, 1, 2 mg tabs | C | 1-4 mg PO tid ^{10,11} | 199.90 |
| <i>Prandin</i> (Novo Nordisk) | | | | 385.20 |
| Thiazolidinediones | | | | |
| Pioglitazone – generic | 15, 30, 45 mg tabs | C | 15-45 mg PO once/d ¹² | 16.70 |
| <i>Actos</i> (Takeda) | | | | 258.60 |
| Rosiglitazone – generic | 2, 4, 8 mg tabs | C | 4-8 mg PO once/d or divided bid ¹³ | N.A. |
| <i>Avandia</i> (GSK) | | | | 117.00 |
| GLP-1 Receptor Agonists | | | | |
| Exenatide – immediate-release | | | | |
| <i>Byetta</i> (BMS/AstraZeneca) | 250 mcg/mL (1.2, 2.4 mL prefilled pen) | C | 5 or 10 mcg SC bid ^{14,15} | 395.50 ¹⁶ |
| extended-release | | | | |
| <i>Bydureon</i> (BMS/AstraZeneca) ¹⁷ | 2 mg powder for injectable suspension | C | 2 mg SC 1x/week ¹⁵ | 407.50 |
| Liraglutide – <i>Victoza</i> (Novo Nordisk) ¹⁷ | 6 mg/mL (3 mL prefilled pen) | C | 1.2 or 1.8 mg SC once/d ¹⁸ | 357.10 ¹⁹ |
| DPP-4 Inhibitors | | | | |
| Alogliptin – <i>Nesina</i> (Takeda) | 6.25, 12.5, 25 mg tabs | B | 25 mg PO once/d ²⁰ | 283.80 |
| Linagliptin – <i>Tradjenta</i> (Boehringer Ingelheim) | 5 mg tabs | B | 5 mg PO once/d | 283.80 |
| Saxagliptin – <i>Onglyza</i> (BMS) | 2.5, 5 mg tabs | B | 2.5-5 mg PO once/d ²¹ | 278.90 |
| Sitagliptin – <i>Januvia</i> (Merck) | 25, 50, 100 mg tabs | B | 100 mg PO once/d ²² | 283.80 |

Table 3. Some Insulin Products

| | | Some Available Formulations ¹ | Onset | Peak | Duration | Pregnancy Category ² | Cost ³ |
|--|--|--|-----------|-----------------|-----------|---------------------------------|-------------------|
| Rapid-Acting | | | 10-30 min | 30 min-3 hrs | 3-5 hrs | | |
| Insulin aspart – | | | | | | | |
| <i>Novolog</i> (Novo Nordisk) | | 10 mL vial, 3 mL cartridge, 3 mL <i>FlexPer</i> ⁴ | | | | B | 168.20 |
| Insulin glulisine – <i>Apidra</i> (Sanofi) | | 10 mL vial, 3 mL <i>Solostar</i> | | | | C | 156.80 |
| Insulin lispro – <i>Humalog</i> (Lilly) | | 10 mL vial, 3 mL cartridge, 3 mL <i>KwikPer</i> ⁴ | | | | B | 167.70 |
| Regular Insulin | | | 30-60 min | 2½-5 hrs | 4-12 hrs | | |
| <i>Humulin R</i> (Lilly) | | 10 mL vial ⁵ | | | | B | 90.80 |
| <i>Novolin R</i> (Novo Nordisk) | | 10 mL vial | | | | B | 90.70 |
| Intermediate-Acting | | | 1-2 hrs | 4-8 hrs | 10-20 hrs | | |
| NPH – | | | | | | | |
| <i>Humulin N</i> (Lilly) | | 10 mL vial, 3 mL <i>KwikPer</i> ⁴ | | | | B | 90.80 |
| <i>Novolin N</i> (Novo Nordisk) | | 10 mL vial | | | | B | 90.70 |
| Long-Acting | | | | | | | |
| Insulin detemir – | | | | | | | |
| <i>Levemir</i> (Novo Nordisk) | | 10 mL vial, 3 mL <i>FlexPer</i> ⁴ | 1-4 hrs | relatively flat | 12-20 hrs | B | 191.30 |
| Insulin glargine – | | | | | | | |
| <i>Lantus</i> (Sanofi) | | 10 mL vial, 3 mL <i>SoloStar</i> | 1-4 hrs | no peak | 22-24 hrs | C | 191.30 |
| Pre-Mixed | | | | | | | |
| <i>Novolin 70/30</i> (Novo Nordisk) | | 10 mL vial | 30-60 min | 2-12 hrs | 18-24 hrs | B | 90.70 |
| (70% NPH, human insulin isophane susp and 30% regular human insulin injection) | | | | | | | |
| <i>Novolog Mix 70/30</i> (Novo Nordisk) | | 10 mL vial, 3 mL <i>FlexPer</i> ⁴ | 10-20 min | 1-4 hrs | 18-24 hrs | B | 174.40 |
| (70% insulin aspart protamine susp and 30% insulin aspart injection) | | | | | | | |
| <i>Humalog Mix 75/25</i> (Lilly) | | 10 mL vial, 3 mL <i>Pen</i> , 3 mL <i>KwikPer</i> ⁴ | 10-30 min | 1-6½ hrs | 14-24 hrs | B | 173.80 |
| (75% insulin lispro protamine susp and 25% insulin lispro injection) | | | | | | | |

1. Available in a concentration of 100 units/mL.

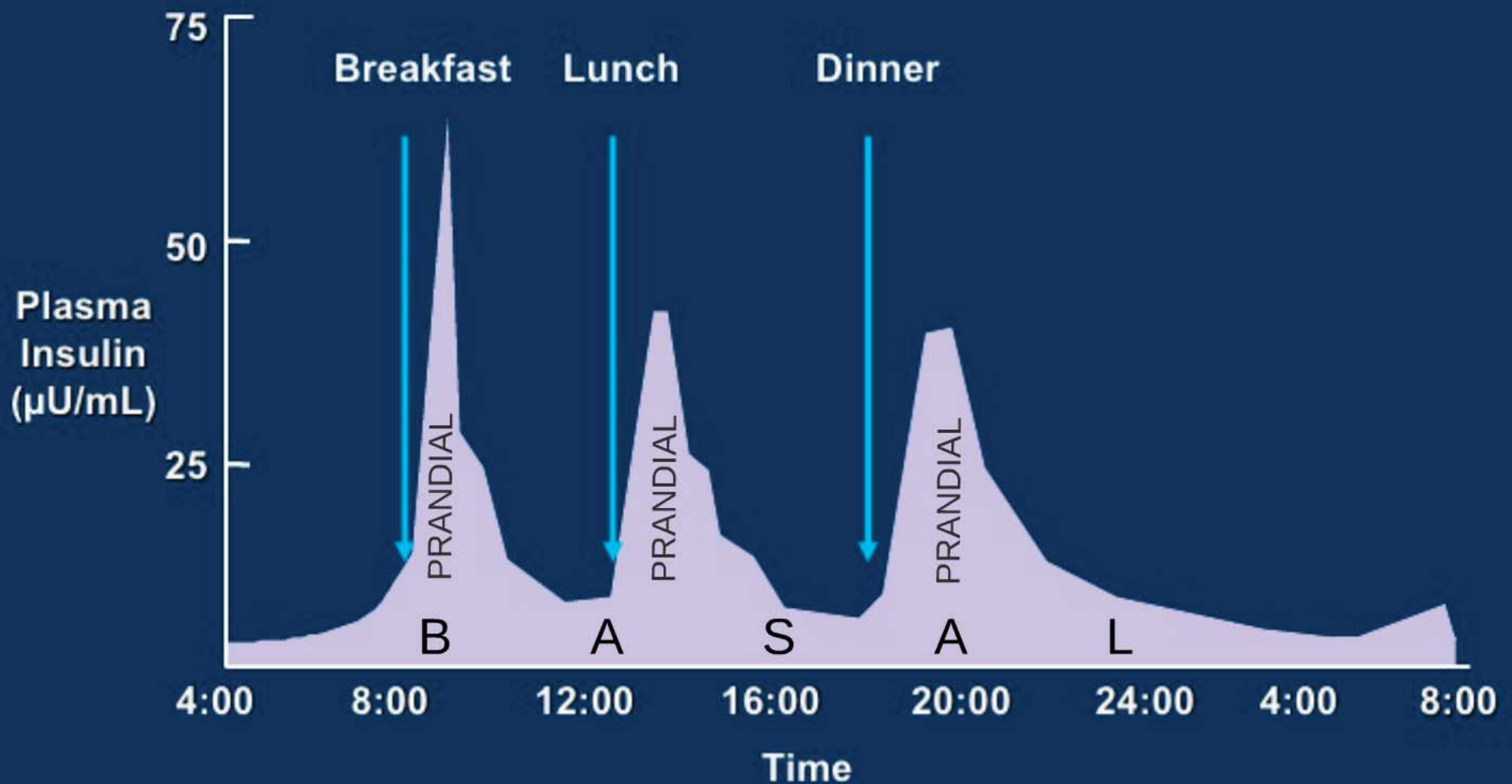




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HTN, Gout, GERD, DM2,
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HbA1c 9.1%

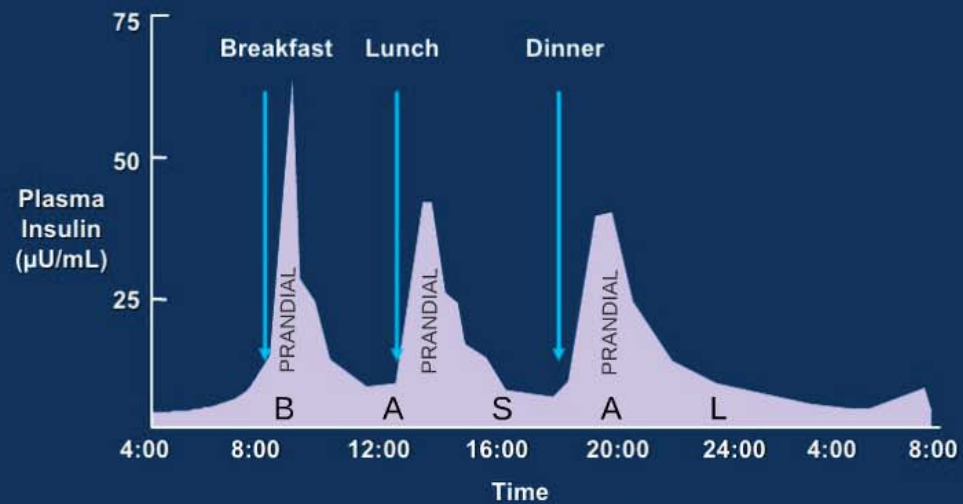


Physiologic Blood Insulin Secretion Profile



Adapted from White JR, Campbell RK, Hirsch I. Postgraduate Medicine. June 2003;113(6):30-36.

Physiologic Blood Insulin Secretion Profile



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7

Insulin Analog Dosing

Basal: ~1 unit per hour

Prandial: Insulin:CHO Ratio

Mono-therapy

Efficacy⁺
Hypo risk⁺
Weight⁺
Side effects⁺
Costs⁺

Dual therapy[†]

Efficacy⁺
Hypo risk⁺
Weight⁺
Side effects⁺
Costs⁺

Triple therapy**Combination injectable therapy[‡]**

Healthy eating, weight control, increased physical activity, and diabetes education

Metformin

high
low risk
neutral / loss
GI / lactic acidosis
low

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

| Metformin + | Metformin + | Metformin + | Metformin + | Metformin + | Metformin + |
|--|---|--|---|--|--|
| Sulfonylurea | Thiazolidinedione | DPP-4 inhibitor | SGLT2 inhibitor | GLP-1 receptor agonist | Insulin (basal) |
| high efficacy moderate risk weight gain hypoglycemia low costs | high efficacy low risk weight gain edema, HF, fxs low costs | intermediate efficacy low risk neutral weight rare side effects high costs | intermediate efficacy low risk weight loss GI, dehydration high costs | high efficacy low risk weight loss GI high costs | highest efficacy high risk weight gain hypoglycemia variable costs |

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

| Metformin + | Metformin + | Metformin + | Metformin + | Metformin + | Metformin + |
|---|---|--|--|---|---|
| Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin [§] | Thiazolidinedione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin [§] | DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin [§] | SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin [§] | GLP-1 receptor agonist + SU or TZD or Insulin [§] | Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA |

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

Metformin +

Basal insulin + Mealtime insulin or GLP-1-RA