Pharmacological Management of Diabetes

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Disclosure

I do not have/had financial interest/arrangement or affiliation with one or more organizations that could be perceived as a related or apparent conflict of interest in the context of the subject of this presentation

Diabetes Mellitus

- Is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both

- Type 2 diabetes may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance

CDA 2013 Guidelines; Can J Diabetes. 2013;37(suppl 1):S1-S212.

Time Line of Diabetes

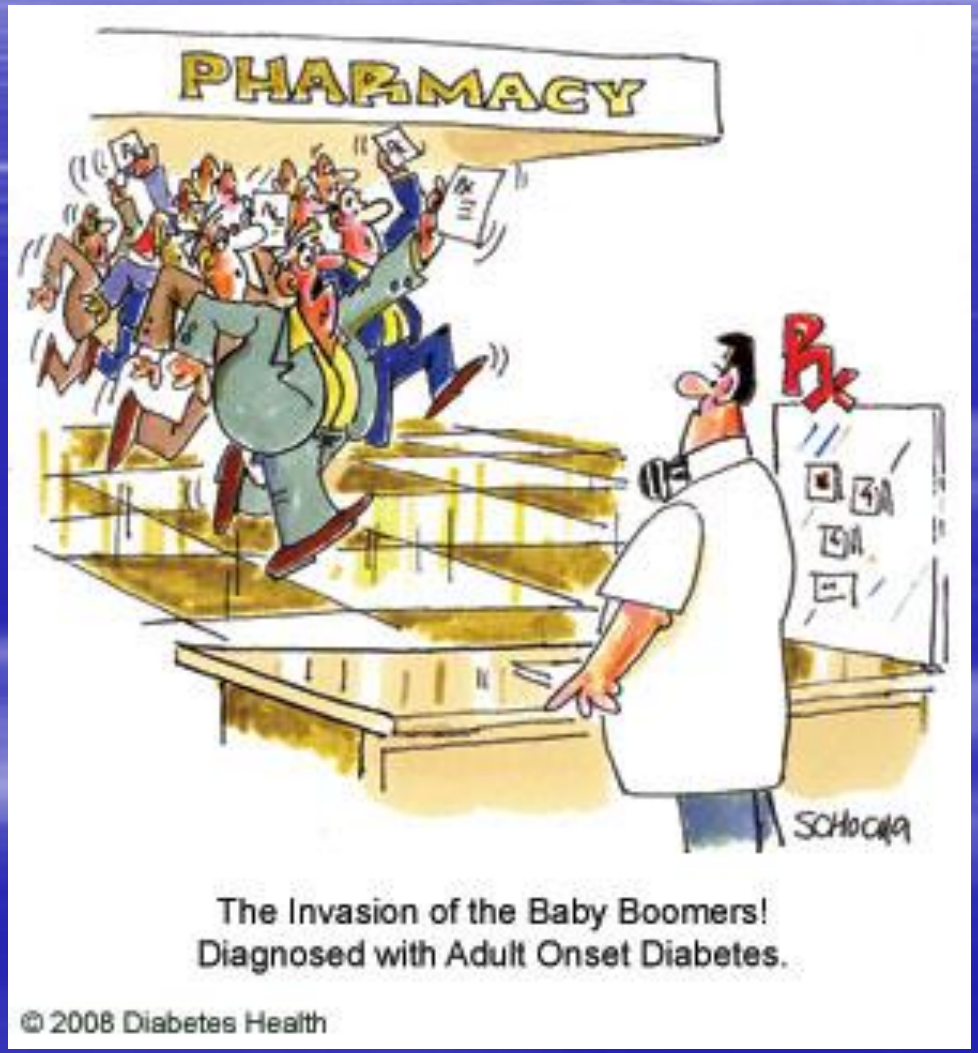
Frequent urination	1552 BC
Term `Diabetes`	250 BC
Distinction of 2 types DM	1776 AD
Ìslets of Langerhans`	1869
Term Insulin	1909
Bantings work	1920
1st Insulin extract used on 14 y.o. boy	1922
`NPH insulin developed	1938
Oral drugs developed	1955
DM 1 & DM2 classified	1959
1st BG strip developed	1964
1st Pancreas Transplant	1966
1st BG meter and pump	1970
A1C test	1976
Biosythetic insulin	1983
DCCT trial	1993
Acarbose	1995
Humalog	1996
UKPDS study	1998
Gluconorm	1999
TZDs Avandia	2000
Lantus	2002
Levemir	2005
1st DPP-4 Januvia	2008
Byetta, Victoza	2010

Diabetes: Scope of the Problem

- ~ 371 **million people** worldwide affected
- ~ 1 in 10 people or 3 cases/sec or ~552 million by 2030
- ~10% DM1, DM2 dramatically increasing
- For every 2 people known DM one is undiagnosed
- ~80% of people with DM will die as a result of heart disease or stroke
- Direct costs for medication & supplies ranging from $1,000 to $15,000 a year.
- By 2020 it's estimated that diabetes will cost the Canadian healthcare system **$16.9 billion a year**

CDA 2013 Guidelines; Can J Diabetes. 2013;37(suppl 1):S1-S212.

The Surge of Type 2 Diabetes



What are Treatments for Diabetes?

1. Nutrition
2. Physical Activity
3. **Insulin**
4. **Oral Medications - Type 2**
5. Others (eg. Pancreatic transplant)

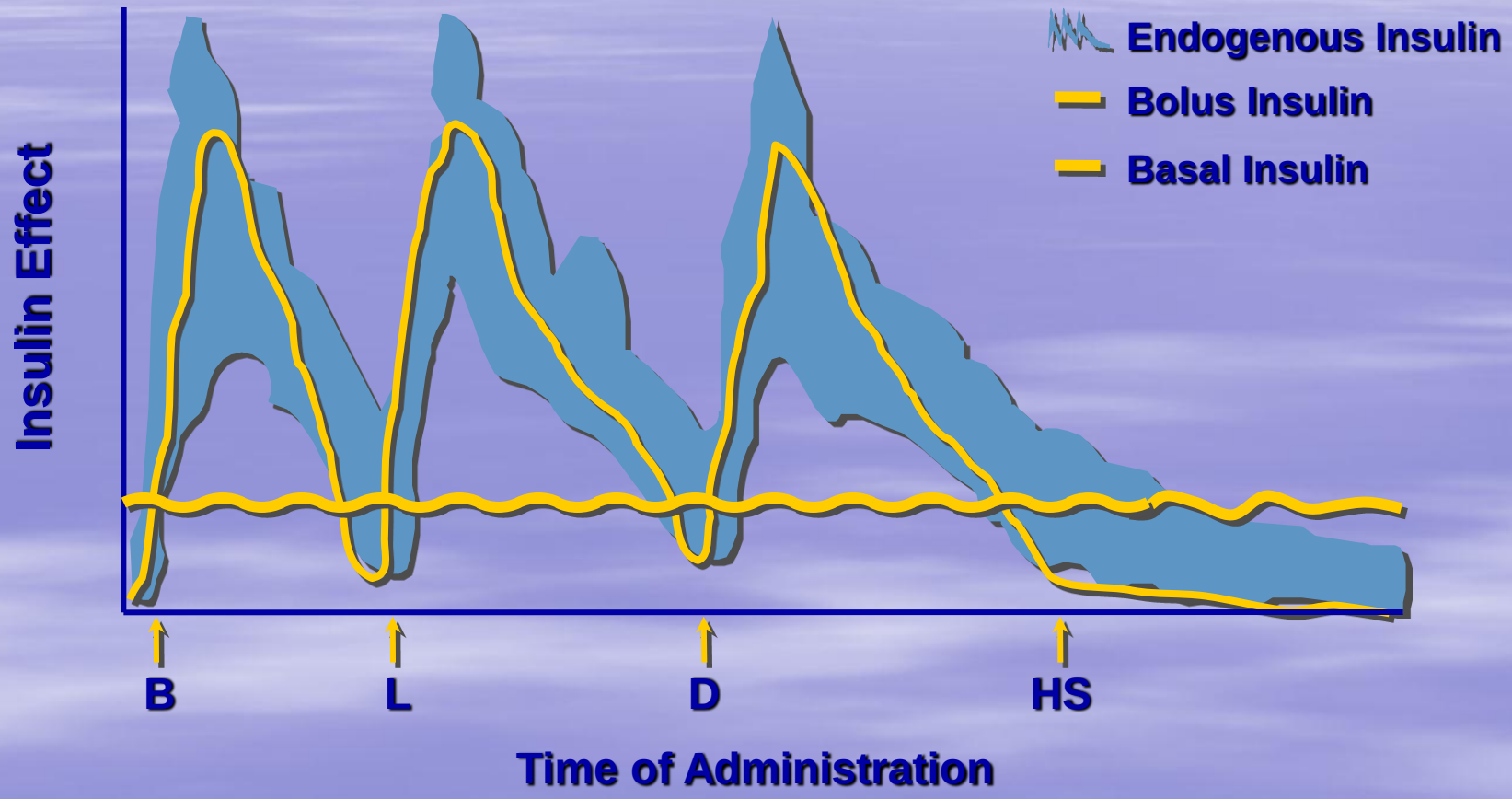
Goals of Pharmacologic Therapy

- To attain optimal glycemic control
- To prevent or delay the onset and progression of complications
- To achieve individual satisfaction & quality of life
- To minimize potential adverse events related to treatment

Functions of Insulin

- Stimulates glucose uptake & metabolism by muscle & adipose cells
- Inhibits glucose output by liver (gluconeogeneis)
- Inhibits hydrolysis of triglycerides in adipose tissue (glycolysis)
- Stimulates amino acid uptake & protein synthesis
- Inhibits protein degradation in muscle & other cells
- Regulates gene transcription in numerous cell types

Normal Insulin Secretion: The Basal-Bolus Insulin Concept

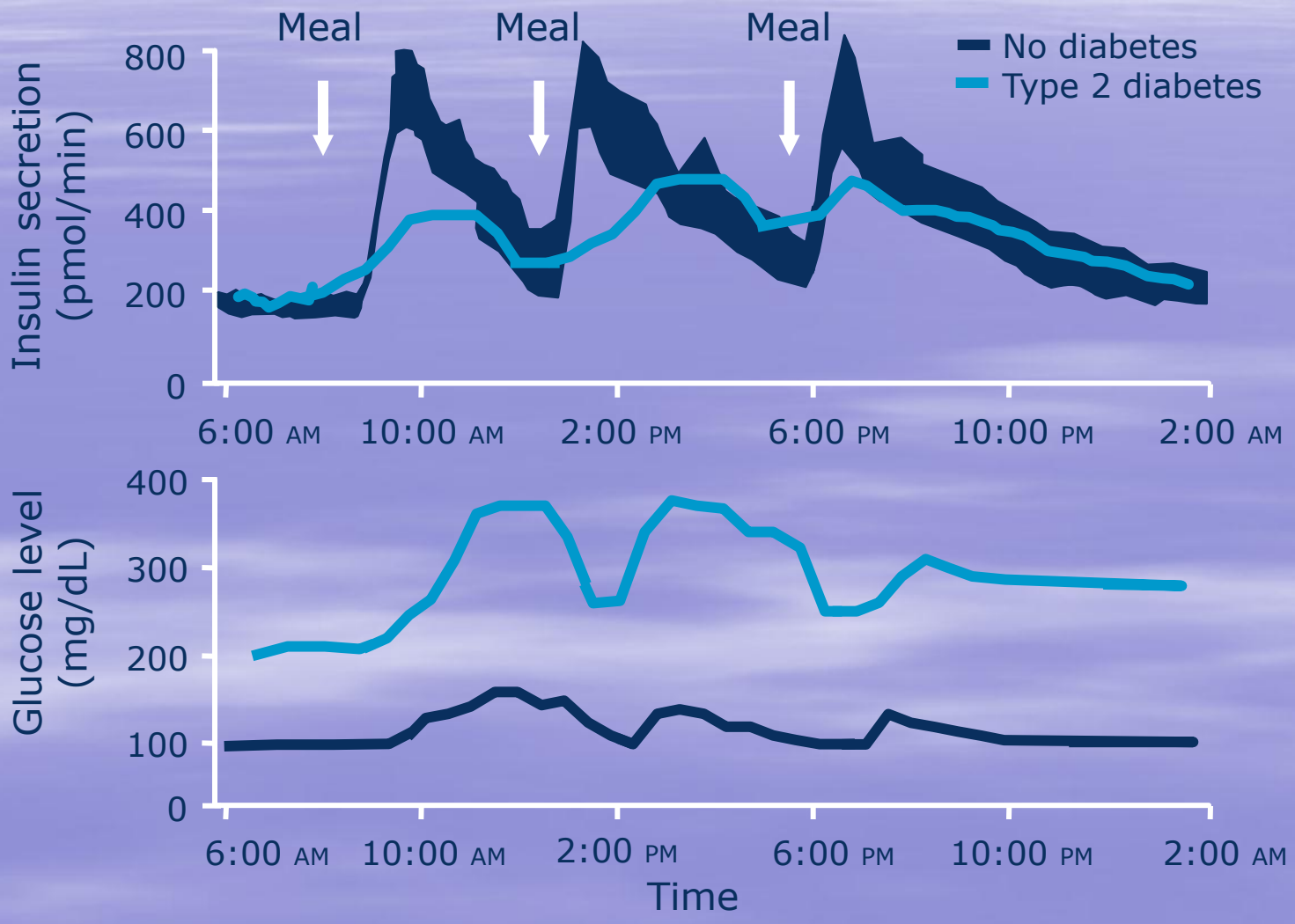


B, breakfast; L, lunch; D, dinner; HS, bedtime.

Adapted from:

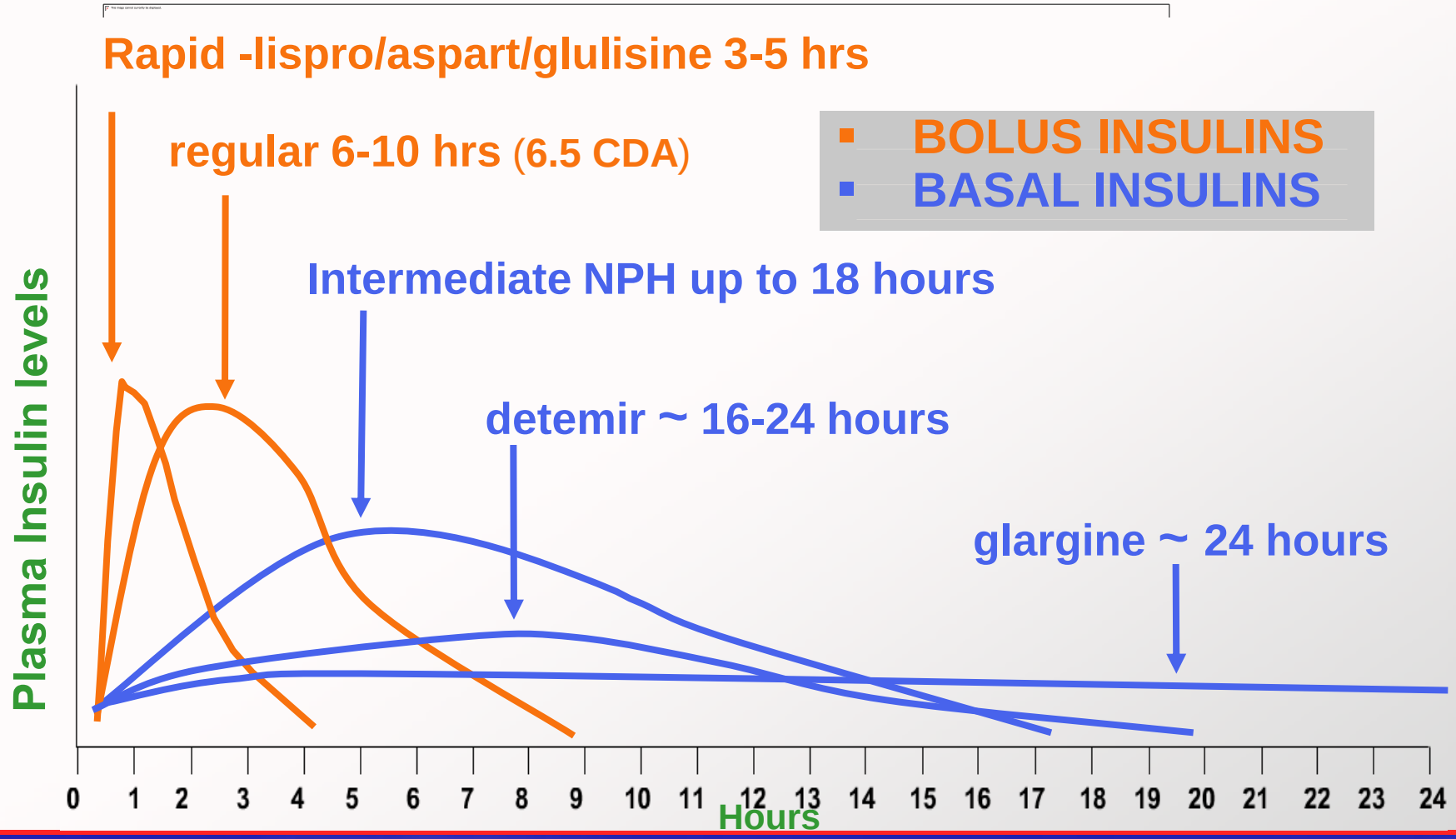
1. Leahy JL. In: Leahy JL, Cefalu WT, eds. *Insulin Therapy.* New York, NY: Marcel Dekker, Inc.; 2002.
2. Bolli GB et al. *Diabetologia.* 1999;42:1151-1167.

In type 2 diabetes, mealtime insulin secretion is blunted and delayed



Polonsky K, et al. *N Engl J Med* 1996;334:777

Insulin Action Profiles



Note: action curves are approximations for illustrative purposes. Actual patient response will vary.

Mayfield, JA.. et al, Amer. Fam. Phys.; Aug. 2004, 70(3): 491

Plank, J. et.al. Diabetes Care, May 2005; 28(5): 1107-12

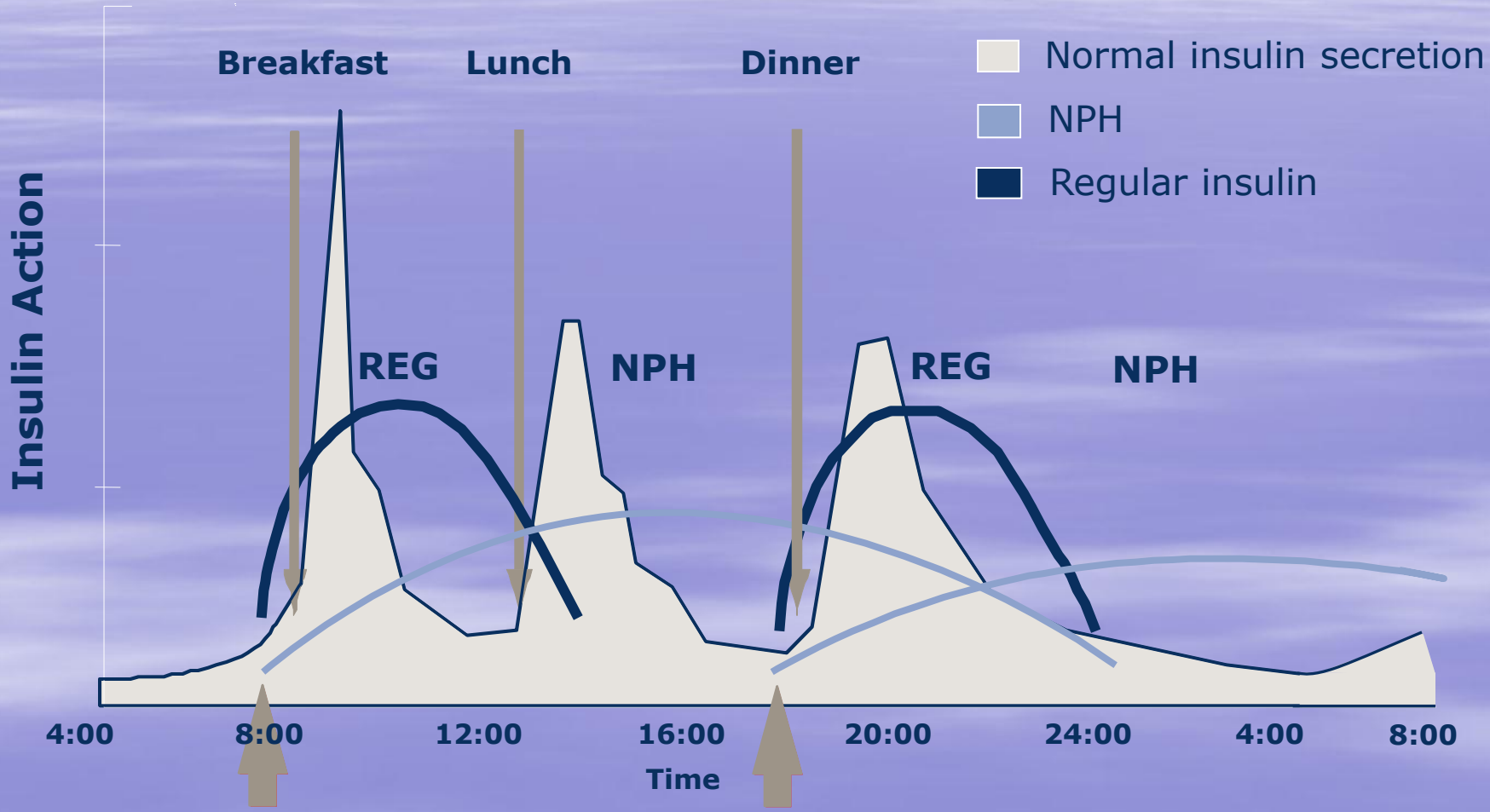
Available Insulin

Type	Name	Starts to work in:	Peak Action	Duration
Rapid acting analog	Lispro (Humalog) Aspart (NovoRapid) Glulisine (Apidra)	10-15 min 10-15 min 10-15	1-2 hr 1-1.5 hr 1-1.5 hr	3-5 hrs 3.5-4.75 hrs 3-5 hrs
Short acting	Regular (R,Toronto)	30-60 min	2-3 hrs	6.5 hrs
Intermediate acting	NPH (N) Humulin N	1- 3 hrs	5-8 hrs	Up to 18 hrs
Premixed human (%R%N)	30/70,40/60,50/50	30-45 min*	4-8.6 hrs*	10-16 hrs*
Premixed analog	Humalog Mix 25, Mix 50 NovoMix 30	5-15 min*	4-8.5 hrs*	10-16 hrs*
Long acting analog	Glargine (Lantus)	90 min	No Peak	24 hrs
	Detemir (Levemir)	90 min	Blunted peak	16-24 hrs

CDA 2013 Guidelines, Can J Diabetes. 2013;32(suppl 1) except for *

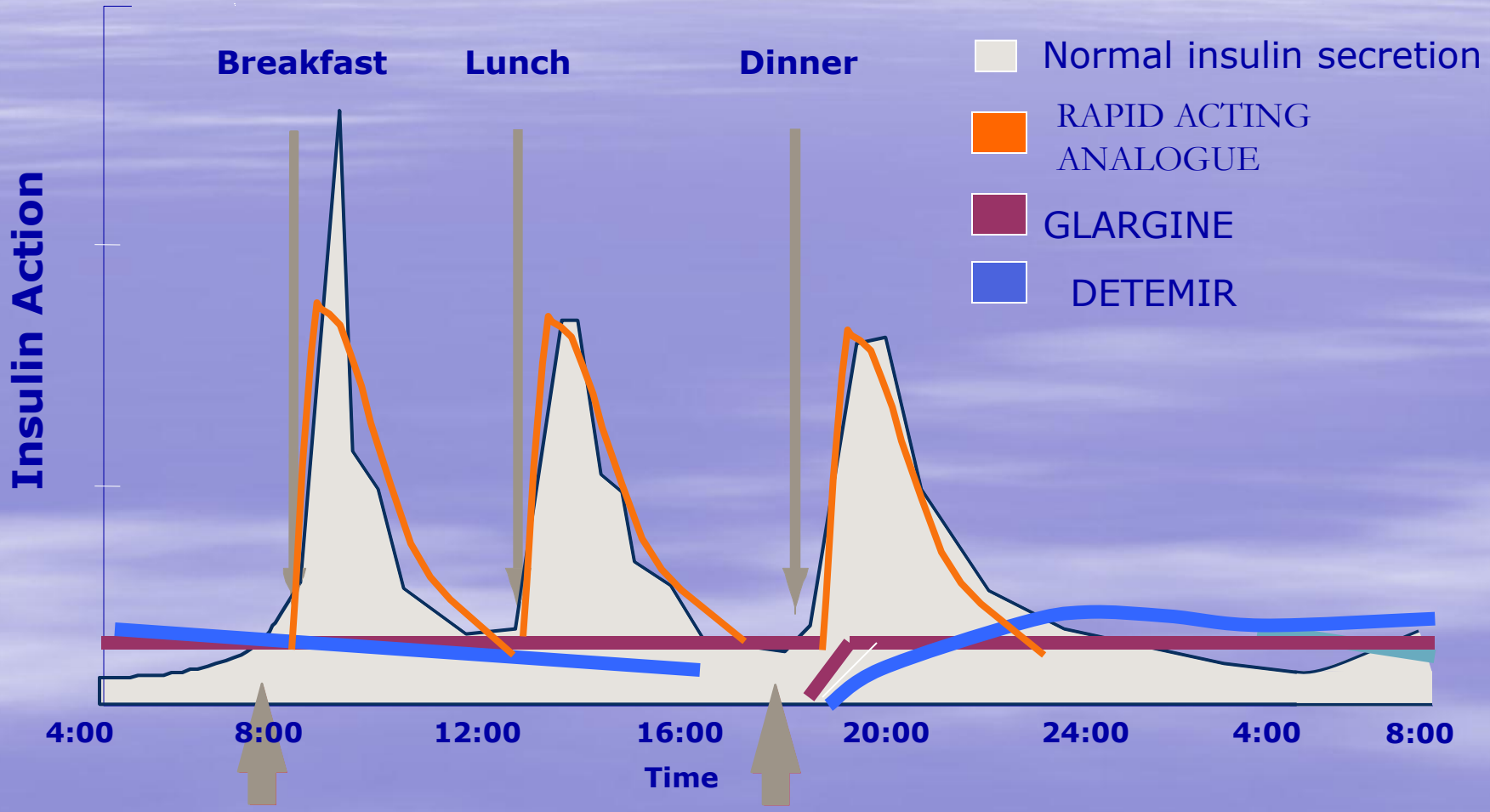
*Pearson J &Powers M.: Systematically Initiating Insulin. The Diabetes Educator 2006; 32; 19-28S

Regular and NPH Insulin



Adapted from Leahy J. In: Leahy J, Cefalu W, eds. *Insulin Therapy.* New York, NY: Marcel Dekker; 2002:87; Nathan DM. *N Engl J Med.* 2002;347:1342–1349.

Analogue Insulin – rapid & long-acting



Adapted from Leahy J. In: Leahy J, Cefalu W, eds. *Insulin Therapy*. New York, NY: Marcel Dekker; 2002:87; Nathan DM. *N Engl J Med*. 2002;347:1342–1349.

Fear of the Needle

Injection Devices

Vial and Syringe

Reusable Insulin Pens for Insulin Cartridges

NovoPen 4

NovoPen Echo – replaces Jr

Sanofi ClikSTAR refillable Pens

Silver Lantus Purple Apidra

Pre-filled Lantus and Apidra Solostar

Lilly Pens

Lilly Pre-filled Kwikpen at bottom

Insulin Pens

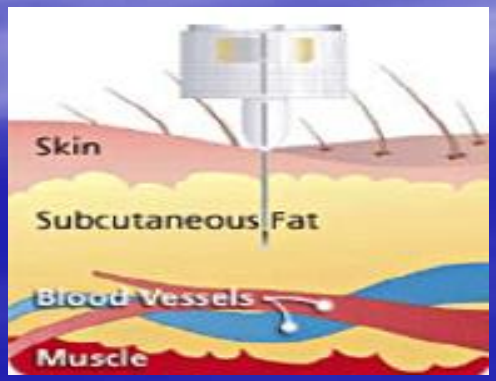
- Consult directions with each pen
- New needle tip for each injection
- Re-suspend cloudy insulin, tap to send any air bubble to needle end
- Prime with a 2 unit shot each time, a drop of insulin should appear, repeat until a drop appears.
- Dial dose & perform injection
- Remove and discard needle tip – do not store with needle tip on

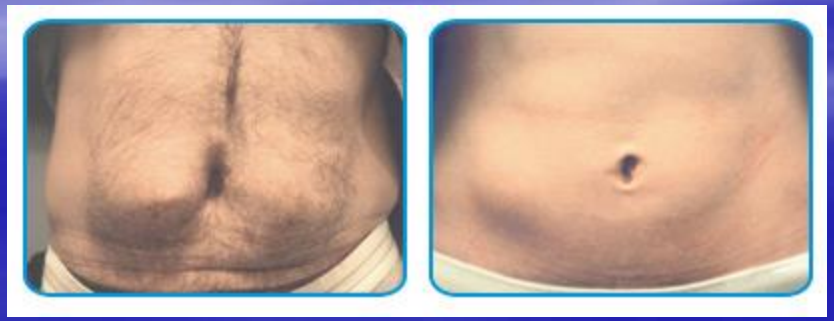
Injections

Because he knew the importance of daily injection site rotation, George went to extremes to avoid problems.

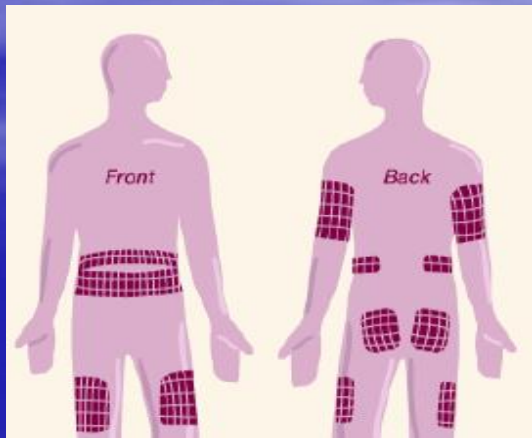
Injections

- New syringe/needle tip with each injection- avoids lipohypertrophy (see middle below)
- Regardless of BMI – Needle length 6mm or less
- Subcutaneous injection, if necessary pinch up skin
- Count to 10 before removing needle
- Abdomen has fastest most consistent absorption followed by upper arm, thighs, buttock
- Rotate site daily. Avoid the area 2 inches around the belly button.





Lipohypertrophy



Vial and Syringe

- Re-suspend cloudy insulin by gently rolling between hands or rocking gently back and forth 10-20 times. DO NOT SHAKE
  - Improperly mixed cloudy insulin can lead to substantial variability
  - Small study showed only 9% mixed NPH properly before injection
- Draw air into syringe equal to dose of insulin & inject into vial
- Hold vial upside down and withdraw correct dose of insulin plus a little extra
- Check for bubbles tap syringe, expel any bubbles and the extra insulin
- Remove needle from vial and perform injection

Barnett AH. A review of basal insulins. *Diabet Med*. 2003;20:873-885

Storage

- Unopened Vials – Refrigerate between 2-8º C until expiry date do not place on door or near freezer compartment
- Once opened keep at room temperature for 28 days (room temperature injections are less painful) Once opened discard at end of specified interval whether room temperature or refrigerated
  - Humulin and Humalog NovoRapid, Lantus < 30º C
  - Apidra < 25ºC
  - Novolin < 25ºC
  - Levemir < 30ºC for 42 days
- Inspect appearance
  - clear insulin should be clear
  - cloudy insulin should not be clumped
- Prior to use cloudy insulin should be adequately re-suspended by gently rolling between hands or gently rocking back and forth 10-20 times. Avoid excess shaking to prevent clumping and muting of effect

Insulin Dose

DM1 Insulin intensive therapy:

- Typically 0.3-0.5 units/kg
- 40% TDID basal, 20% bolus 3x a day

DM2 adding basal with oral agents:

- Initiate at a dose of 0.1 to 0.2 units/kg of body weight
- Alternatively can initiate with 10 units at bedtime
- Titration is 1 unit per day until fasting BG 4-7 mmol/L
  - May need to go slower…patient specific

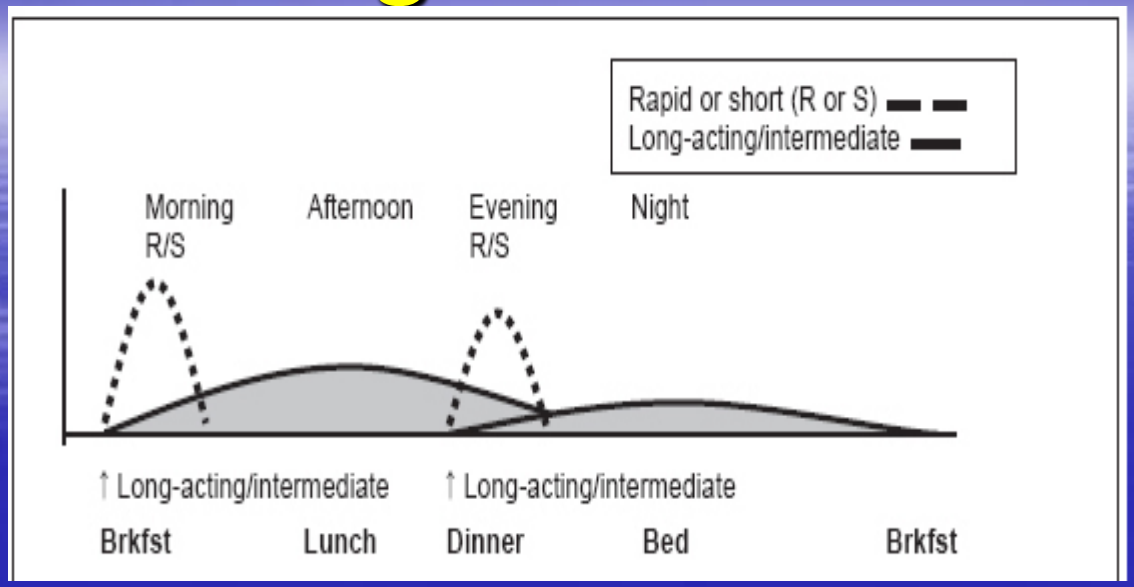
Premixed (30/70, Mix 25,50, or added to oral agents):

- Start 5-10 units once or twice daily (or lower)
- Increase by 1-2 units till BG target reached pre-meal

Factors in Regimen Selection

- Not everyone can use the most optimal regimen
- Must consider many factors:
  - Expected duration & quality of life
  - Patients treatment goals
  - Self-management skills
  - Socioeconomic
  - Lifestyle
  - Regimen should minimize frequency of hypoglycemia
  - Regimen should avoid severe hypoglycemia
  - Others

Regimen - Conventional



TDID = 60U
2/3 Breakfast = 40U
1/3 Supper = 20U

Breakfast:
2/3 INT = 27U
1/3 RA/SA = 13U
} 40U

Supper:
2/3 INT = 13U
1/3 RA/SA = 7U
} 20U

- For DM2, consistent schedule
- 2/3 TDID before breakfast, 1/3 before supper
- 2/3 insulin INT, 1/3 SA/RA

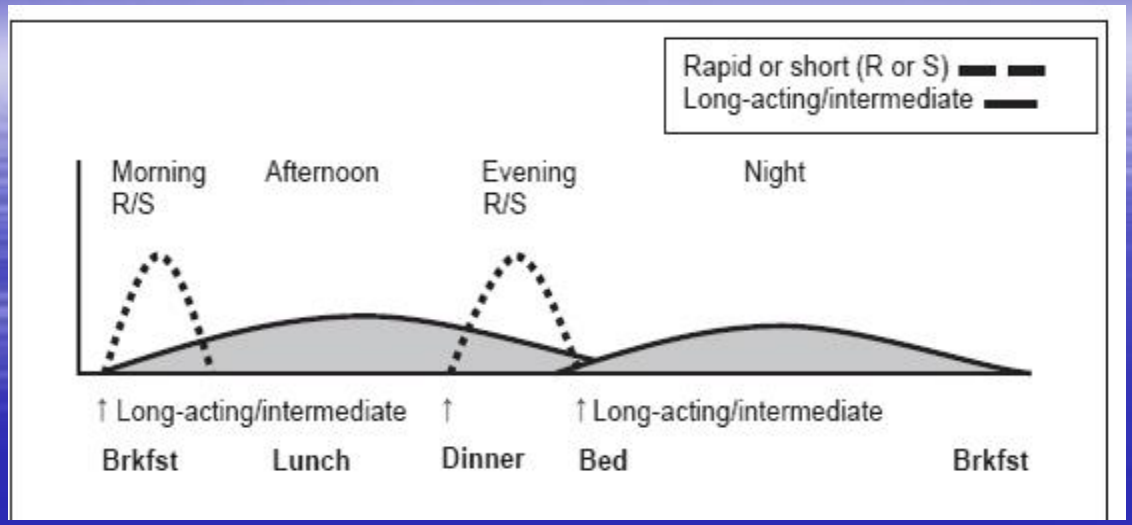
Benefits

- Simple
- 2 injections
- Can teach to adjust

Limitations

- No mealtime flexability
- ↑ Risk nocturnal hypo
- No 'fine tuning'
- Day time control difficult

Regimen - MDI 3 Injections/day



TDID = 60U
2/3 Breakfast = 40U
1/3 Supper = 20U

Breakfast: Same
27 INT, 13 RA

Supper:1/3 RA/SA = 7U
Bedtime: 2/3 INT = 13U

- RA/SA+INT still at breakfast, RA/SA Supper, INT at HS
- 2/3 insulin dose before breakfast, 1/3 split supper and HS
- 1/3 SA/RA alone at supper, 2/3 INT given HS

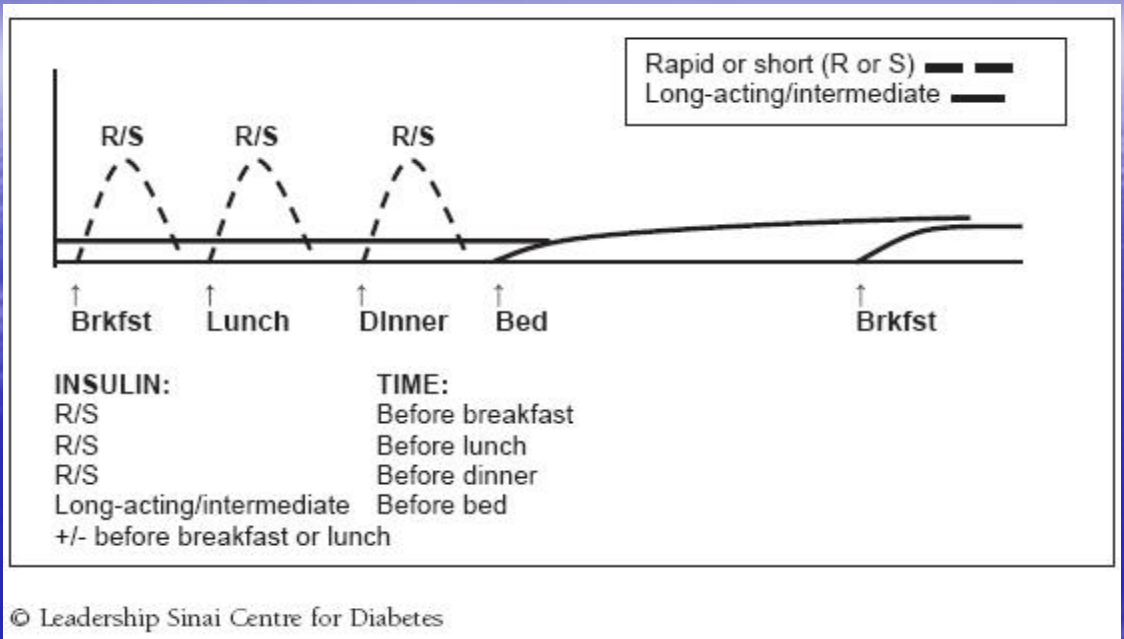
Benefits

- ↓ Risk nocturnal hypo
- ↑ Flexibility to change doses
- Can Δ INT/LA to target FBG

Limitations

- Lack daytime flexibility
- May need between meal snacks

Regimen - MDI 4-5 Injections/day



TDID = 60U
40% basal = 24U INT/LA
At bedtime

60% RA/SA = 36U
Split 35%B, 30%L, 35%S

Breakfast = 13U
Lunch = 10U
Supper = 13U

- 40-50% TDID basal (INT/LA)
- 50-60% pre-prandial (SA/RA): 35%B, 30%L, 35%S

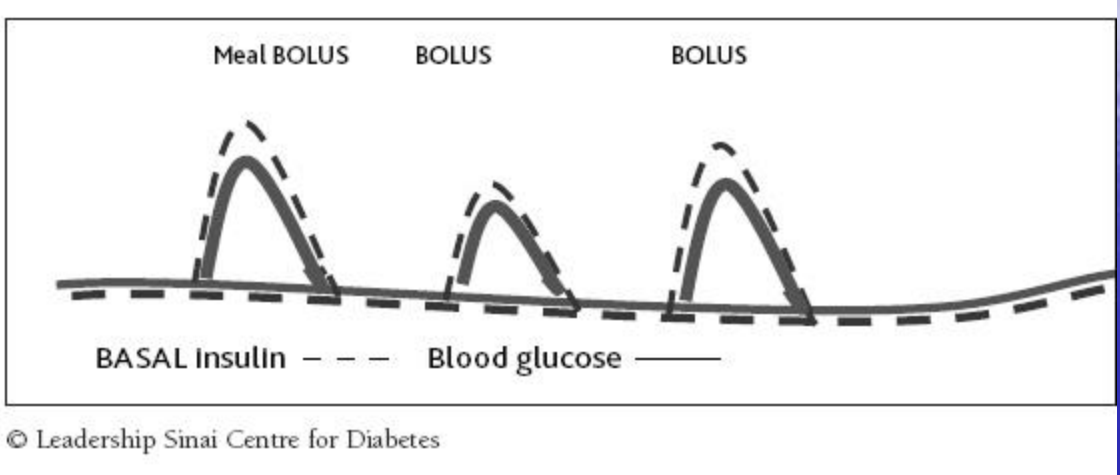
Benefits

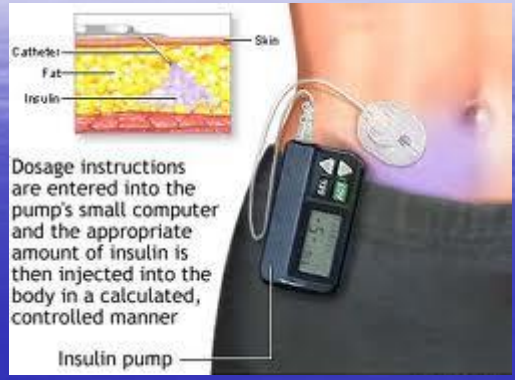
- ↓ Risk midday/nocturnal hypo
- ↑ Flexibility to change doses
- Can target prandial & FBG

Limitations

- 4-5 injections/day
- Frequent blood monitoring
- $$
- Needs DHCT support

Regimen - Pump Therapy





- RA/SA insulin given on continual basis to mimic pancreas
- Premeal 'bolus' depends on meal, BG, CHO & activity

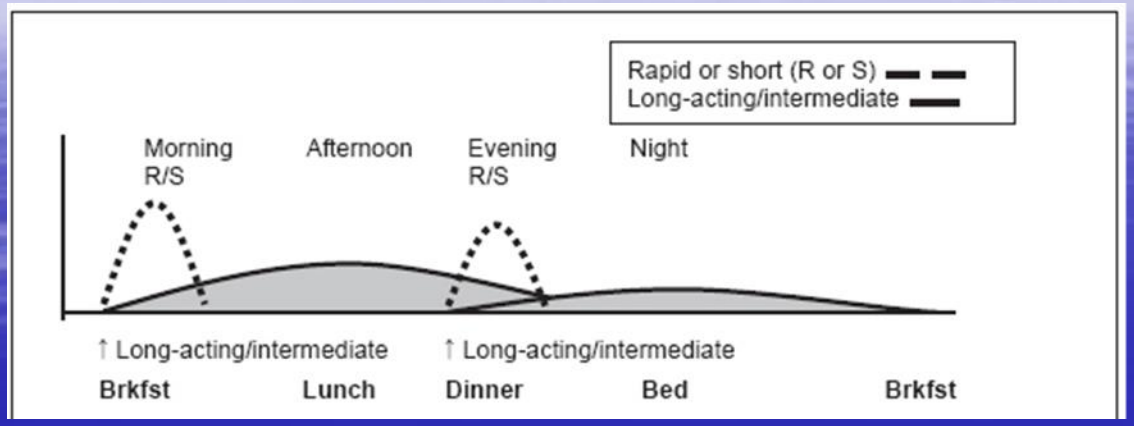
Benefits

- ↓ Day - day variation in absorp
- ↑↑ Flexibility to change doses
- Eliminates MDI's
- Can bolus in between meals

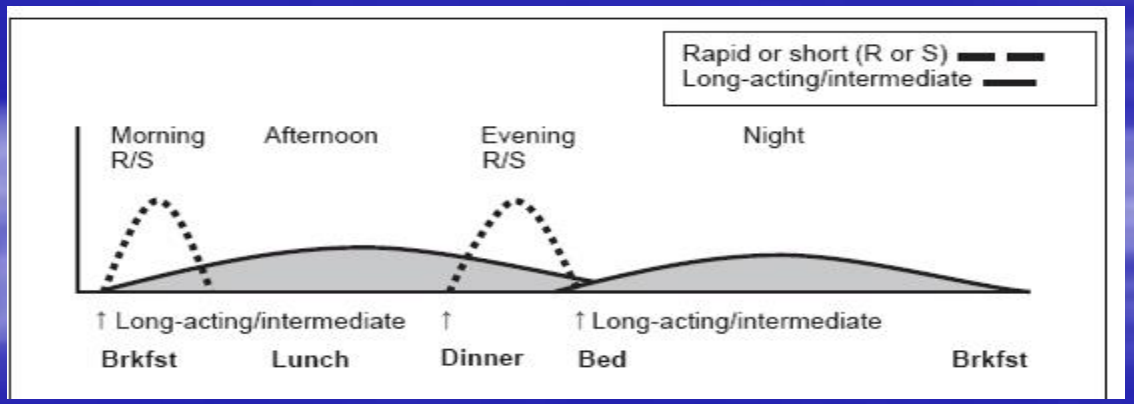
Limitations

- Needs motivation, ability
- ↑ Risk Hyperglycemia & DKA
- $$$$$$$$$
- Needs DHCT support

Example – Regimen Change

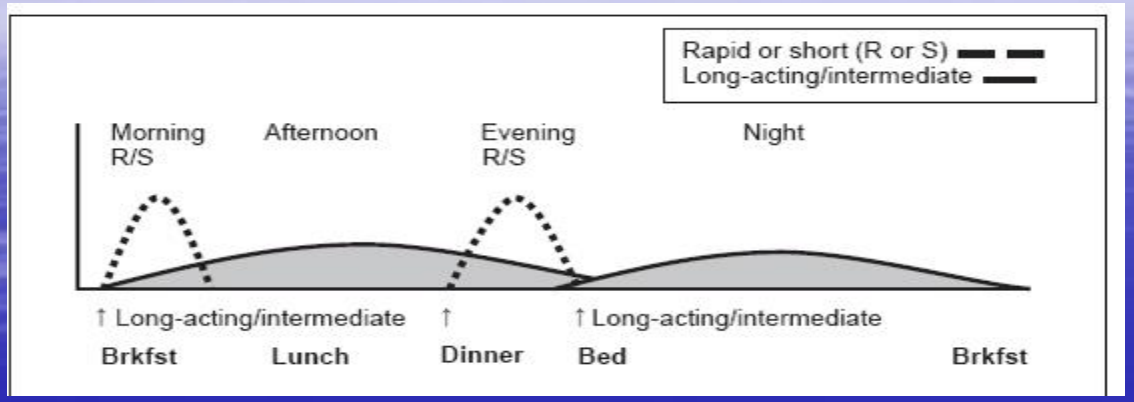


- 30/70: 25 AM, 20 Supper
- Lows 2-3AM
- Highs in AM
- 2hr after supper good

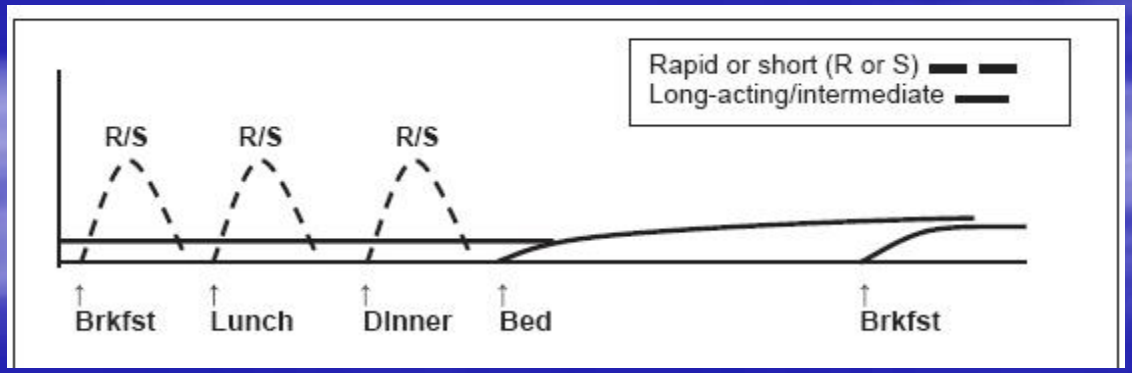


- Maintain 30/70: 25 AM
- 7U SA Supper
- Move 13U INT bedtime

Example – Regimen Change



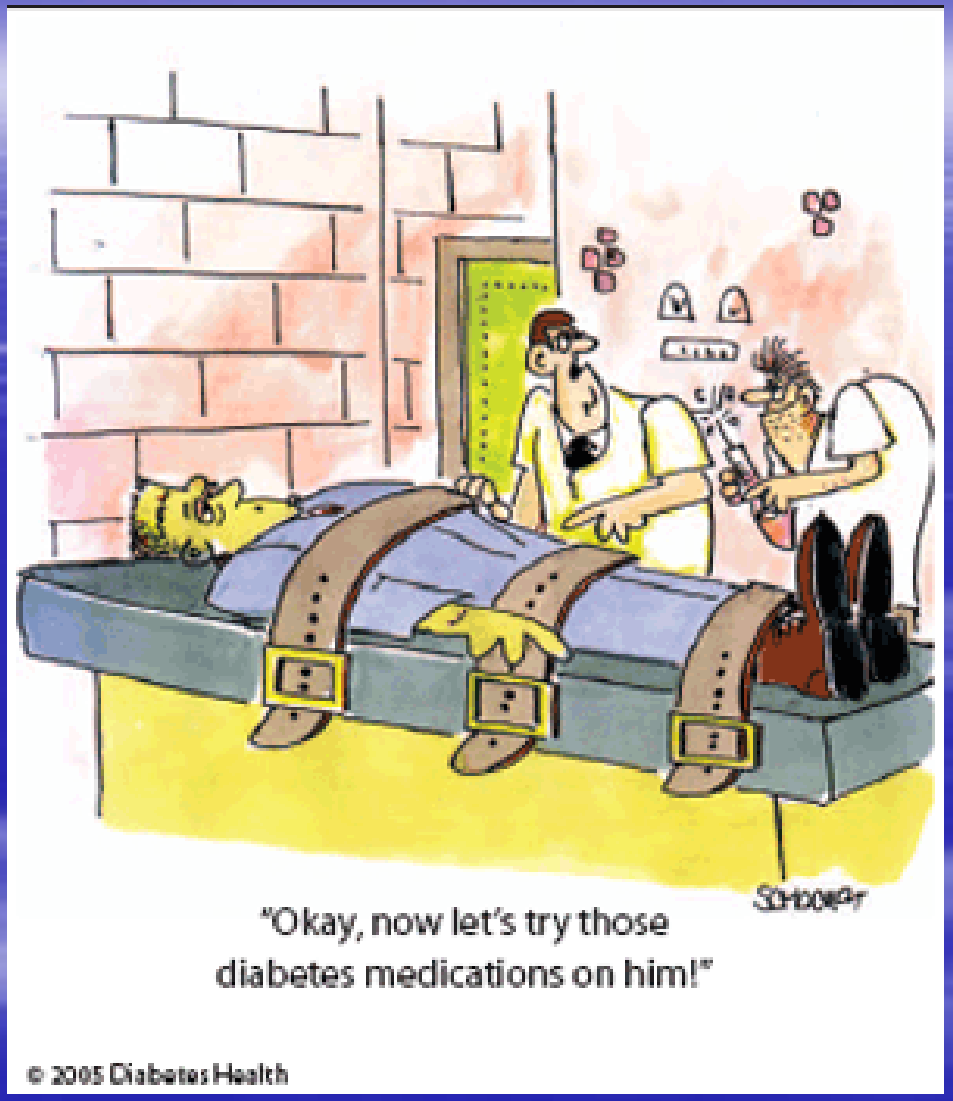
- 30/70: 25 AM, 7U SA Supper, 13U INT bedtime
- Fasting OK, 2hrs after breakfast OK
- Pre-lunch, 2hr post-lunch consistently elevated



- 45U/day 50% basal = 23U INT or LA
- 22U pre-meals divided 35%B, 30%L, 35%S = 8U at breakfast, 7U Lunch, 8U supper
- May consider 10% ↓ in TDID b/c regimen more physiological

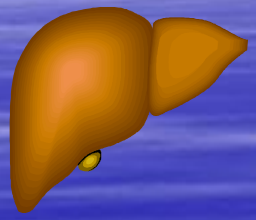
Principles in Adjusting Insulin Dose

- Blood glucose levels reflect prior insulin dose(s)
- Check BG at times related to the insulin action:
  - Eg. Lantus check fasting…can ↑ or ↓ by 1-2 units accordingly
  - Eg. 2hr post-meal reflects RA insulin
- Adjust 1 insulin at a time
- Adjust 1 dose at a time
- Adjust dose by 1 or 2 units at a time or 10%
- Look at BG pattern:
  - Address hypo`s first
  - Fasting
  - Pre-prandial
  - Post prandial



"Okay, now let's try those diabetes medications on him!"

Oral Medication targets

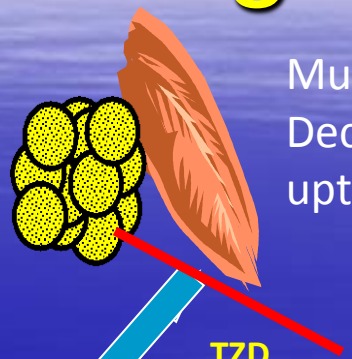


LIVER
increased glucose production

Metformin

(TZD)

Insulin



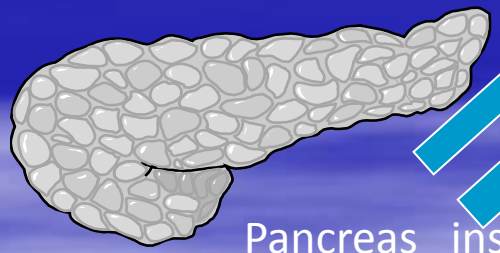
Muscle and Fat Cells
Decrereased peripheral gluco
uptake (insulin resistance)

TZD

(Metformin)

insulin

Lower Blood Sugar Levels



Pancreas insulin secretion

glucagon suppression

Sulfonylureas

Meglitinides

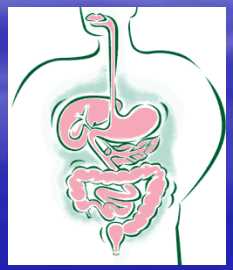
Insulin

GLP-1, DPP-4 inhibitor

Gut Carbohydrate delivery and absorption

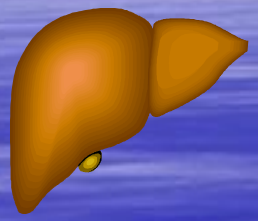
Alpha-glucosidase inhibitor

GLP-1, DPP-4 Inhibitor



Sites of Action

LIVER



↓Hepatic Glucose Production

biguanides

thiazolidinediones

DPP-4 inhibitors

GLP-1 analogues

INTESTINE

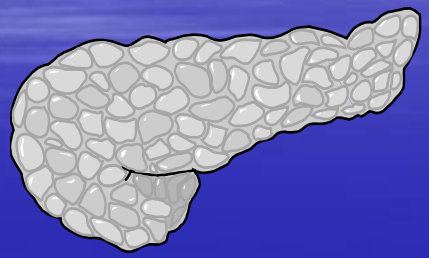
Slow CHO Absorption

alpha-glucosidase inhibitors

Slow GI Motility

GLP-1 analogues

PANCREAS



↑Insulin Secretion

sulfonylureas

nonsulfonylureas

DPP-4 inhibitors

GLP-1 analogues

↓ Glucagon Secretion

DPP-4 inhibitors

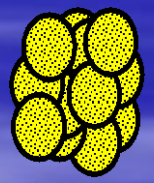
GLP-1 analogues

BRAIN

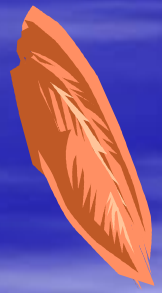
↑ Satiety

GLP-1 analogues

ADIPOSE TISSUE



MUSCLE



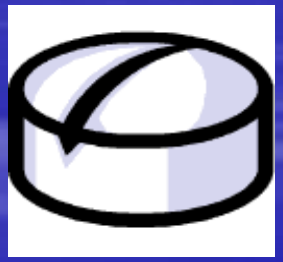
↑Peripheral Glucose Uptake

thiazolidinediones

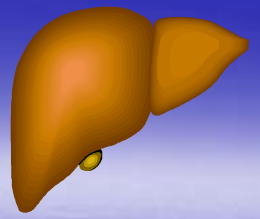
biguanides

Six Classes of Oral Hypoglycemics and GLP-1 Analogues

- Biguanides
- Thiazolidinediones
- Alpha-Glucosidase Inhibitors
- Sulfonylureas
- Nonsulfonylureas (meglitinides)
- DPP-4 Inhibitors
- GLP-1 Analogues

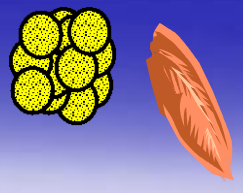


Target: Liver



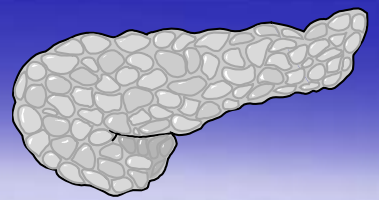
- Biguanide: Metformin –1st choice medication DM2
  - Decreases sugar output from liver
  - Secondary effect increased peripheral sugar uptake
- Start 500mg BID or 850mg QD & slowly titrate up
- Minimize GI upset by taking with largest meals or use long acting form (Glumetza) to reduce side effects
- See ↓ FBG in 3-5 days, 1-2 weeks for maximal effect
- BG lowering effect peaks out ~1500mg/day
- Nausea, vomiting, diarrhea, headache, agitation, sweating, weight loss, decreased vitamin B12 levels (1500mg daily for more than 3 years), Lactic Acidosis
- Does not cause hypoglycemia
- Effective:
  - Decreases Fasting Blood Sugar 3-3-3.9 mmol/L
  - Lowers A1C 1.0-1.5 %
  - ↓ LDL & TG, slight ↑ HDL

Target: Muscle/Fat Cells



- Thiazolidinediones (TZD's):
  Rosiglitazone (Avandia), Pioglitazone (Actos)
- Decreases peripheral insulin resistance, ↑ BG uptake in muscle cells
  Secondary – decreases glucose output from liver
- Not 1st-line b/c of risk of edema, wt. gain, CHF, fractures & CV outcomes
- Avandia 2-8mg daily, Actos 15-45mg daily, without regard to food
- BG lowering starts in 2 weeks, 6-12 for maximal effect
- Does not cause hypoglycemia
- Not approved for combination use with insulin
- Liver monitoring required. No dose adjustments for renal insufficiency
- Side effects: upper respiratory tract infections, fluid retention, heart failure
- Clinical effects:
  - Decrease Fasting blood sugar 2.2 -3.3 mmol/L
  - Decrease A1C 1.0-1.5%
  - Avandia ↑ HDL (~10%), LDL, +/- TG, Actos ↑ HDL (~10%), ↔LDL, ↓ TG 10-20%

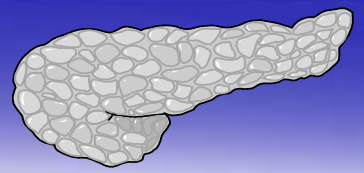
Target Pancreas



Sulfonylureas: Glyburide (Diabeta), glicazide (Diamicron), glimepiride (Amaryl)

- Stimulate insulin secretion in beta cells in presence of glucose
  - Glyburide: 2.5-5mg QD to start and titrate. 10mg BID max
    - Take ½ hour before meals…must have regular carbohydrate intake
  - Gliclazide: Usually MR formulation. Start 30mg QD with breakfast and titrate q 1 -2 weeks. Swallow whole. 120mg max
  - Glimepiride: Start 1mg QD and titrate q 1-2 weeks. 8mg/d max. Take with breakfast or first meal
- Side Effects: Hypoglycemia, weight gain (2-3kg), sulfa allergy, avoid glyburide in renal failure
- 3rd gen agents gliclazide (lowest hypo incidence) & glimepiride are more glucose dependent- less hypoglycemia than glyburide but $
- Clinical Effects:
  - Decreases Fasting Blood Sugar 3.3-3.9 mmol/L
  - Decreases A1C 1.0-1.5%
  - No effect LDL, TG, HDL

Target Pancreas



Non-sulfonylureas – Meglitinides: Repaglinide (Gluconorm), Nateglinide (Starlix)

- Stimulate short term glucose dependent insulin release
  - Requires functioning beta cells.
  - Rapid onset peaks in 1 hour duration 4 hours
  - Restores 1st phase insulin release, blunting postprandial glucose excretion
  - Option if allergic to sulfonylureas

- Repaglinide: Start at 0.5-1mg TID with each meal. Titrate weekly. Then at 1st bite or 15-30 min prior to meal. Must dose adjust for elderly. Avoid with gemfibrozil.

- Nateglinide: Start at 60-120mg QD-TID before meals. Titrate weekly to a maximum of 180mg TID. No dose adjustment in elderly.

- These meds are good for irregular meal times…more flexible
  - No meal = no pill

- Side Effects: hypoglycemia but less than sulfonylureas, weight gain (less)

- Clinical Effects:
  - Reduces after meal blood sugar peak by 3.3 mmol/L
    Reduces A1C 1% for repaglinide, .5% for nateglinide

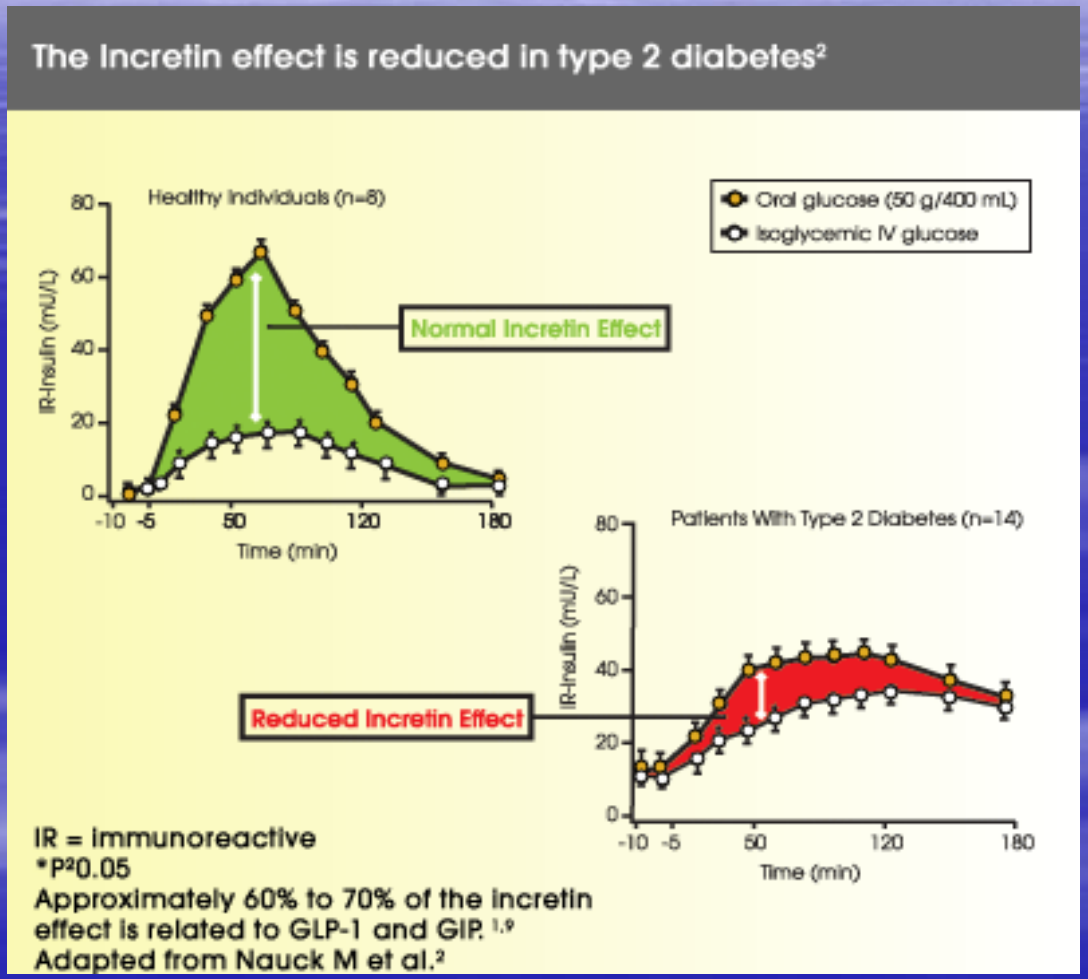
Target Gut

- Alpha-glucosidase inhibitor – acarbose (Glucobay)
- Blocks α-glucosidase in brush border of small intestine that converts carbs to monosaccharides
  - Delays carbohydrate absorption and reduces postprandial BG
- Dosing: Start with 25mg QD-TID & titrate slowly by 25mg/day q 2-4 weeks as tolerated to max of 100mg BID-TID. Take with first bite of meal. No dose adjustment until CrCl < 25 mL/min
- Peaks out in effect at ~ 50mg TID; higher doses - side effects
- Side Effects: 30% Gastrointestinal: gas, abdominal discomfort, cramps. 80% Gas.
- Does not cause hypoglycemia but must treat hypos with pure sugar, such as milk, honey or dextrose tabs
- Clinical Effects:
  - Reduces after meal blood sugar by ~2.8 mmol/L
  - Reduces A1C 0.5-1%
  - No effect on LDL, HDL, slight ↓TG's

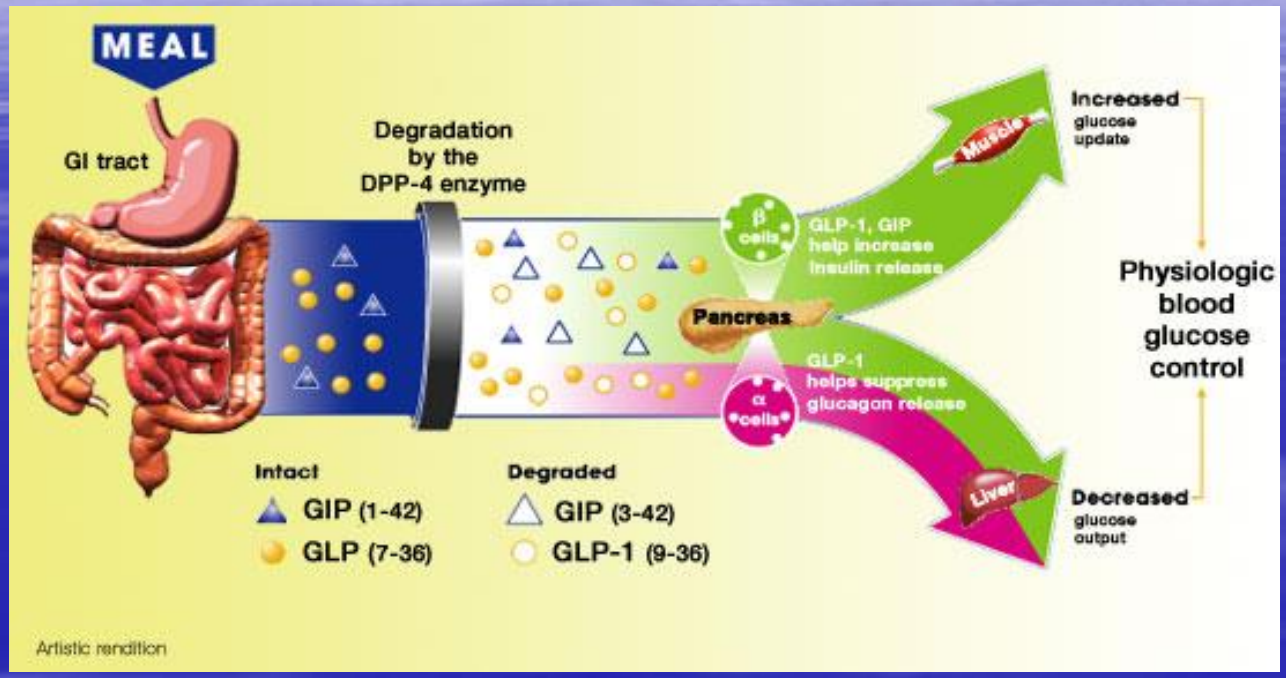
Target Gut – New Incretin Therapies

- Incretin Hormones
  - GLP-1 Glucagon-like Peptide 1
  - GIP Gastric Inhibitory Polypeptide
- Produced by GI tract in response to carbohydrate intake
- Discovered when insulin response to oral glucose was noted to exceed response to IV glucose

Reduced Incretin Effect in Patients With Type 2 Diabetes



Role of Incretins to Reduce Glucose



- Glucose dependent stimulation of insulin secretion
- Glucose depended suppression of glucagon secretion
- Slowing of gastric emptying
- Improvement in beta cell function & preservation
- In animal studies increase in beta cell mass
- Feeling of satiety, reduced food intake
- Weight loss

www.incretin.com.tw

Target Gut: Incretin Mimetics

- THESE ARE NOT ORAL AGENTS
- Exenatide (Byetta) -Synthetic form of a protein found in the saliva of the Gila monster that mimics the actions of (GLP-1)
- Liraglutide (Victoza)– Human GLP-1 An analogue closer in structure to native GLP-1 than exenatide
- Injectable therapy used in Type 2 DM using sulfonylurea, metformin or combination of both
- Altered when made to be more resistant to DPP-4 degradation
  - Increases their half-life and duration of action

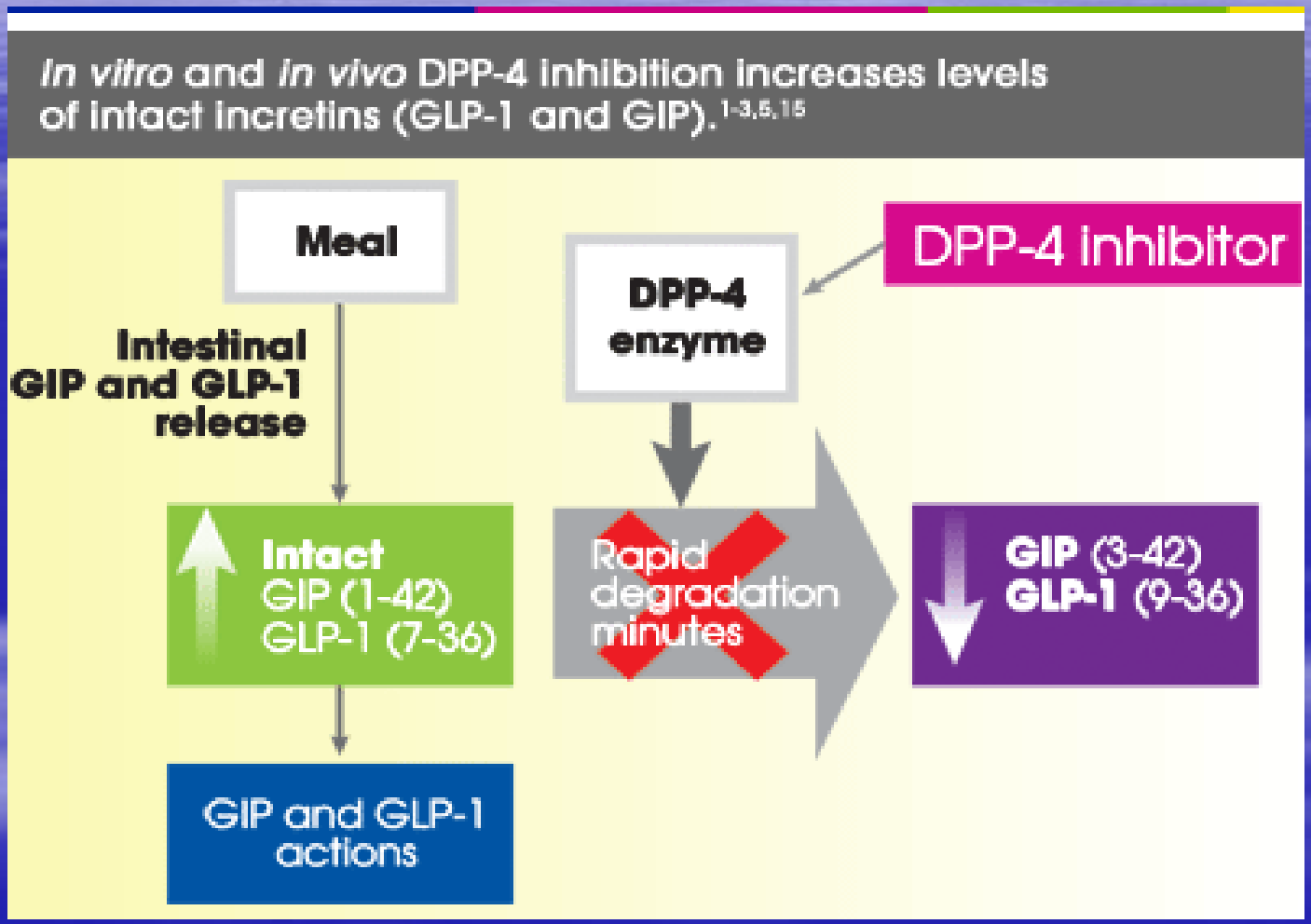
Target Gut – Incretin Mimetics - Byetta

- Approved January 2011
- Approved in combo with MET +/or a SULF in pts with DM2 when MTD oral therapies + diet & exercise inadequate
- NEW: With glargine (+/- MET) when glargine, diet & exercise inadequte
- Available as: 5 or 10mcg pre-filled pens (Fridge, prime once)
- Start at 5mcg SQ BID & titrate to 10 mcg BID after 1month
  - No dose adjustment with MET, 50% dose with SULF
  - Nausea, GI side effects (40 – 50%) limit ability to titrate
  - Vomiting (13%), Diarrhea (13%), Dizziness, Headache (9%)
  - Causes hypoglycemia in combo with SULF
- Taken < 60 min before meals. No meal or forgot = no dose
- No dose adjustment in elderly, not used if CrCl is < 30mL/min
- Can worsen gastroparesis & slow medication absorption
- Reduction in post-prandial BG & weight
  - Reduces after meal blood sugar by 2.7 - 4.5 mmol/L
  - Weight loss average 2.5-4 after 1 year; reports of maintained weight loss

Target Gut – Incretin Mimetics - Victoza

- Approved May 2010
- Approved in combo with MET or MET + SULF in pts with DM2 when MTD oral therapies + diet & exercise inadequate
- Available as: 2 x 3mL pre-filled pens 6 mg/mL (Fridge)
  - Multi-dose pen can deliver 30 doses of 0.6mg, 15 of 1.2mg & 10 of 1.8mg
- Start at 0.6mg SQ QD x 1 week, then 1.2mg QD
  - Based on clinical response can increase to 1.8mg QD
  - No dose adjustment with MET, use discretion with MET + SULF (↓ SULF)
  - Nausea, GI effects (~30%) limit ability to titrate; deemed to be less than Byetta
  - Vomiting (~10%), Diarrhea (~17%), Dizziness (~6%), Headache (~9%)
  - Causes hypoglycemia in combo with SULF
- Given once daily, anytime, independent of meals
- Can change injection site and timing without changing dose
- CrCl 30-50mL/min no dose change…do not use if mod – severe
- Reduction in post-prandial BG & weight
  - Reduces after meal blood sugar by 3.3 – 3.9 mmol/L
  - May reduce FPG if given with supper
  - Weight loss average 2 – 3 kg
  - Reduces HA1C 1-1.5%

Target Gut: The DPP-4 Inhibitors



Target Gut – New Class DPP-4 Inhibitors

- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Trajenta)
- Prolongs effect of naturally occurring GLP-1
- Side Effects: most do not experience any side effects
  - Some possible side effects Upper respiratory tract infection, stuffy nose, no effect on weight
- Rarely/no hypoglycemia

Sitagliptin - Januvia

- 1st DPP-4 inhibitor to market, approved December 2007
- Adjunct to diet and exercise, combo with Metformin when diet & exercise plus Metformin inadequate, MET + SULF
- NEW: Add on to premixed/ INT,LA insulin (+/- MET) when inadequate response
- Available as 25, 50, 100mg film coated tabs
- Usual dose: 100mg once daily (AM) with or without food
- Precautions: Dose adjustment in moderate to severe renal insufficiency & elderly:
  - CrCl 30-50mL/min 50mg daily, < 30mL/min 25mg daily
- No dose adjustment in mild to moderate hepatic insufficiency
- Not to be used if pregnant or < 18
- Adverse effects:
  - Stuffy nose(5%), RTI(6%), Headache (5%), diarrhea or abdominal discomfort (3%), nausea (1%). Waiting for long-term safety data
- Reduction in fasting, post-prandial glucose & HA1C:
  - HA1C 0.6-1.4%
  - FBG ~ 1.0 mmol/L & 2hr post-prandial 2.6 mmol/L
- NO Weight gain, rarely hypoglycemia

Saxagliptin - Onglyza

- 2nd DPP-4 inhibitor to market, approved September 2009
- Approved for use in combo with Metformin or a sulfonylurea when metformin + sulfonylurea alone or with diet & exercise inadequate
- NEW: Add on to premixed/ INT,LA insulin (+/- MET) when inadequate response
- Available as 2.5, 5mg film coated tabs
- Usual dose: 5mg once daily (AM) with or without food
- Precautions: Dose adjustment in mod - severe renal insufficiency & elderly:
  - CrCl 30-50mL/min 2.5mg daily, < 30mL/min 2.5mg daily
- No dose adjustment in mild to moderate hepatic insufficiency
- Not to be used if pregnant or < 18
- Adverse effects:
  - Stuffy nose(5%), RTI(6%), Headache (5%), diarrhea or abdominal discomfort (3%), nausea (1%). Waiting for long-term safety data
- Reduction in fasting, post-prandial glucose & HA1C:
  - HA1C ~0.83% with metformin, ~0.72% with sulfonylurea
  - FBG ~ 1.0 mmol/L & 2hr post-prandial 2.6 mmol/L
- NO Weight gain, rarely hypoglycemia

Linagliptin – Trajenta

- New, approved in July 2011
- Approved in adults with DM2 as monotherapy with diet & exercise or combo therapy: with MET, with SULF, or both MET+SULF
- 5mg once daily (film coated tab), with or without meals
- Precautions: Pancreatitis, CHF, PGP or CYP3A4 inducers, immunocompromised pts, pregnancy, nursing women, pediatric (<18), geriatric (≥65), renal or hepatic impairment
- Monitor BG/A1C, Renal/hepatic function before & during
- Adverse effects:
  - Rarely hypoglycemia on it's own, but ↑↑with sulfonylureas
  - Typical headache, nausea, diarrhea
  - Stuffy nose, sore throat
- No dose adjustment with mild-mod renal/hepatic impairment
- Don't use with severe renal/hepatic impairment…no experience
- Reduction in fasting, post-prandial glucose & HA1C:
  - HA1C ~0.44% alone and 0.5% with metformin or a sulfonylurea
  - HA1C ~ 0.72% with combo metformin + sulfonylurea

Review

Agent	Target	A1C reduction	Comment
Biguanide (Glucophage)	Insulin sensitivity FBG	1.0-1.5%	No Weight gain/Hypo
Sulfonylurea (Glyburide)	Post Prandial FBG	1.0-1.5%	↑ risk hypo. Wt gain
Sulfonylurea Gliclazide (Diamicron) Glimepiride (Amaryl)	Post Prandial FBG	1.0-1.5%	Once daily dosing Less hypoglycemia Less weight gain
Meglitinide (Gluconorm)	Post Prandial & FBG	1.0-1.5%	Less hypo/wt gain Flexible in meals
Meglitinide (Starlix)	Post Prandial	0.5%	Less hypo/wt gain Flexible in meals
TZDs Rosiglitazone (Avandia)	Post Prandial & FBG	1.0-1.5%	Edema, CHF, fluid retention , wt gain, CVE
TZDs Pioglitazone (Actos)	Post Prandial & FBG	1.0-1.5%	Edema, CHF, fluid retention , wt gain, CVE
α-Glucosidase inhibitor (Glucobay)	Postprandial	0.4-0.9%	No wt. gain or hypo 30% have GI
DPP-4 inh. Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Trajenta)	Postprandial	~0.6-1.4%	No wt. gain or hypo

What Can Combo Therapy Achieve?

Combination	Decrease in A1C %
Sulfonylurea + Metformin	1.7
Sulfonylurea + Rosiglitazone	1.4
Sulfonylurea + Pioglitazone	1.2
Sulfonylurea + α-glucosidase inhibitor	1.3
Metformin + Rosiglitazone	0.8
Metformin + Pioglitazone	0.7
Rapaglinide + Metformin	1.5
Metformin + Sitagliptin	0.7
Pioglitazone + Sitagliptin	0.7
** Insulin	NO MAXIMUM

- The natural progression of type 2 diabetes suggests that 60% of persons with this disease will eventually require insulin therapy to adequately control blood glucose levels[1]
- It should be explained to all patients with diabetes that insulin will likely be necessary because of the natural progression of beta cell loss and not because of their failure to manage the condition[2]

1. **Wright A, Burden AC et al. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). Diabetes Care. 2002;25:330-336**
2. **Triplitt C,How to Initiate, Titrate, and Intensify Insulin Treatment in Type 2 Diabetes US Pharm. 2007;32(10):10-16**

Initiating Insulin in Type 2

- Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self management. Social and financial aspects should also be considered. There are many options:
  - Starting with a bedtime insulin in addition to oral antihyperglycemic agents
  - Starting with a Premixed insulin
  - Starting with Intensive insulin therapy

CDA 2013 Guidelines; Can J Diabetes. 2013;37(suppl 1):S1-S212.

Initiating Insulin in Type 2 Diabetes Discuss with the patient

- Their initiation regimen
- Type and starting dose of insulin, explain onset, peak, duration, preparation and storage
- Titration schedule, when to check and what blood glucose targets are being used for titration
- Hypoglycemia: symptoms, prevention, treatment
- sick day guidelines
- Injection device, technique, rotation of site
- Follow up to discuss concerns

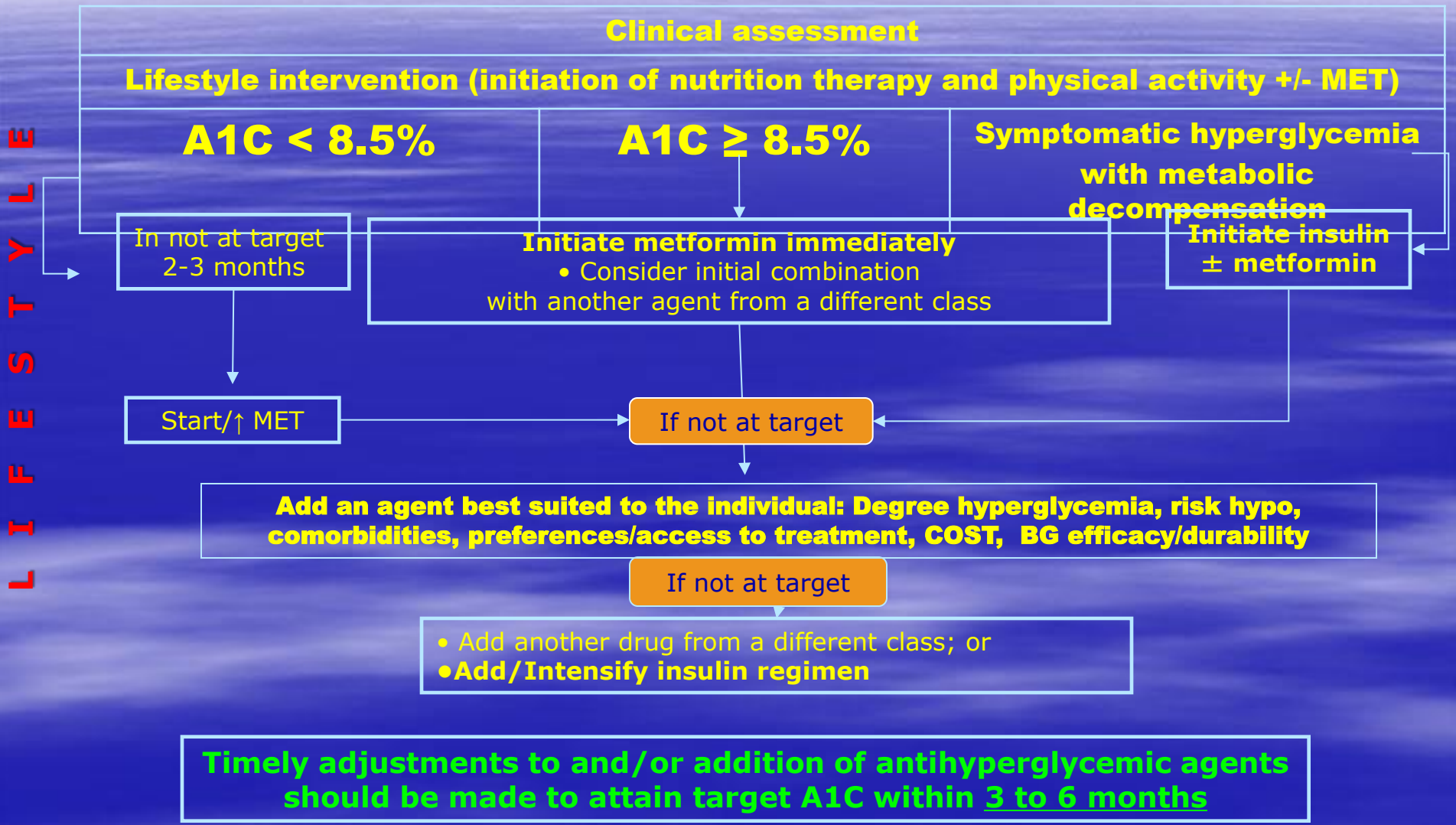
Insulin Initiation in Type 2 Diabetes
Basal added to oral therapy

- Insulin: NPH, Glargine, Detemir
- Starting dose 10 units daily at bedtime
- Titration is 1 unit per day until fasting BG 4-7 mmol/L is achieved. Monitor at least 1/day fasting
- Lower starting, slower titration and higher targets may be considered for elderly or normal weight subjects
- Do not increase dose if person experiences 2 episodes of hypoglycemia in 1 week or any nocturnal hypoglycemia
- Oral antihyperglycemic agents (especially secretagogues) may need to be reduced if daytime hypoglycemia occurs

CDA 2013 Guidelines, Can J Diabetes. 2013;37 (suppl 1) Appendix 3

CDA Practice Guidelines 2013

Management of hyperglycemia in type 2 diabetes



Timely adjustments to and/or addition of antihyperglycemic agents should be made to attain target A1C within 3 to 6 months

CDA. *Can J Diabetes* 2013;37(suppl 1)

Drug-Drug & Drug-Disease Interactions

- Beta-blockers: eg. Propranolol, Bisoprolol, Atenolol
  - Mask signs & Sx hypoglycemia (palpitations, tremor, hunger)
  - Can prolong a hypo episode b/c block countereg hormones
- Steroids: eg. Prednisone, methylprednisone, dexamethasone
  - Increase hepatic glucose synthesis, inhibit peripheral glucose uptake
- Sulfonamides: eg. Bactrim, Septra
  - Potentiate effects & reduce renal clearance of sulfonylureas
- Fluoroquinolones: eg. Ciprofloxacin
  - May increase insulin release from islets of Langerhans cells
- Thiazide Diuretics: eg. HCTZ, indapamide
- Atypical Antipsychotics: olanzapine, quetiaprine, risperidone
  - Increase insulin resistance
- ****ALCOHOL**:**
  - **Reduces glucose synthesis by the liver, reduces glyconeolysis**


"We can control your BG levels.
But I'm afraid you're still going to be goofy!"
© 2005 Diabetes Health

Targets for Blood Glucose Control 2013 Canadian Guidelines

- Glycemic targets should be individualized
- A1C ≤7.0% in order to reduce the risk of microvascular & if implemented early in the course of disease, macrovascular complications
- Less stringent A1C targets (7.1%–8.5% in most cases) may be appropriate in pts with type 1 or type 2 diabetes with any of the following:
  - a) Limited life expectancy
  - b) High level of functional dependency
  - c) Extensive coronary artery disease at high risk of ischemic events
  - d) Multiple comorbidities
  - e) History of recurrent severe hypoglycemia
  - f) Hypoglycemia unawareness
  - g) Longstanding diabetes for whom it is difficult to achieve an A1C ≤7.0% despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy
- FPG or pre-meals 4 to 7 mmol/L
- 2hr post-prandial 5 to 10 mmol/L
- If A1C targets not reached 5-8 mmol/L 2 hrs after meals

CDA 2013 Guidelines; Can J Diabetes. 2013;37(suppl 1).

Hypoglycemia

Causes of Hypoglycemia

- Increase in physical activity
- Taking too much medication
- Missed or delayed meals/snacks
- Eating too little food
- Drinking alcohol without eating

Symptoms of Hypoglycemia

- Neurogenic symptoms are considered ‘warning symptoms’
  - Adrenergic: trembling, palpitations, anxiety, arousal, pallor
  - Cholinergic: sweating, hunger, nausea
- Neuroglycopenic symptoms are more advanced symptoms
  - Sensation of warmth, headache, weakness, fatigue, difficulty thinking, slurred speech, confusion, vision changes, irritability, seizures, coma, brain damage, death

Treatment of Hypoglycemia

Eat or drink 15gm fast-acting CHO

- **5 Dextrosol® or 4 Dex 4®**
- ¾ cup (175 ml) orange juice/regular pop
- 3 tsp (15 ml) honey
- 6 Lifesavers™
- 3 tsp or 3 packets of table sugar dissolved in water

If severe in a conscious person 20gm CHO

In all instances, BG should be retested in 15 min

- Retreat with 15gm CHO if BG less than 4.0mmol/L

Severe unconcsious 1mg glucagon SQ or IM

- Call 911

Treatment of Hypo (cont.)

- Have normal meal or snack
  - If meal or snack is more than 1 hour away, have snack of 15 g CHO and protein
    - 6 crackers with peanut butter/cheese
    - half of a sandwich

Complications

Complications of Diabetes Reduced with 'Tight Control'

- **Microvascular**

  DCCT Study:
  - Retinopathy – ↓ 76% overall, ↓ 54% when disease already present
  - Neuropathy – 69% less occurrence, 57% less when disease already present
  - Nephropathy – 34% less microalbuminuria, 56% less proteinuria

  UKPDS Study:
  - Retinopathy – 21% risk reduction
  - Nephropathy – 34% risk reduction for microalbuminuria

- **Macrovascular**
  - Cardiovascular disease
  - Cerebral vascular disease
  - Peripheral vascular disease
  - DCCT Study showed trend towards reduction risk factor for heart disease (EDIC Study tells more)
  - UKPDS study Heart Disease – 16% reduction- (not significant)
- Topic of future discussion

Questions ???


NATION FACES RISING RATES OF TYPE 2 DIABETES
I'M LEARNING TO MANAGE MY TYPE 2 DIABETES WITH INSULIN!
INSULIN

References

1. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes*. 2013;37(suppl 1):S1-S212.
2. Canadian Pharmacists Association. *Compendium of Pharmaceuticals and Specialties*. Ottawa, ON: CPA; 2012.
3. MedEffect Canada website. Available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php Accessed March 17th 2014.
4. Building Competency in Diabetes Education: The Essentials
5. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New Engl J Med*. 1993;329:977-986.
6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.
7. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317:703-713.

References

8. Advancing Practice. Diabetes Education: A Comprehensive Review.
9. FIT. Forum for Injection Technique Canada. Recommendations for Best Practice in Injection Technique. www.bd.com/ca.
10. Cheng, AY. The Rule of 3's: Insulin Use in Type 2 Diabetes. Canadian Diabetes. Spring 2011;24(1):3-9.
11. Leahy JL. In: Leahy JL, Cefalu WT, eds. *Insulin Therapy.* New York, NY: Marcel Dekker, Inc.; 2002.
12. Bolli GB et al. *Diabetologia.* 1999;42:1151-1167.
13. Polonsky K, et al. *N Engl J Med* 1996;334:777
14. Leahy J. In: Leahy J, Cefalu W, eds. *Insulin Therapy.* New York, NY: Marcel Dekker; 2002:87; Nathan DM. *N Engl J Med.* 2002;347:1342–1349
15. Mayfield, JA.. et al, Amer. Fam. Phys.; Aug. 2004, 70(3): 491
16. Plank, J. et.al. Diabetes Care, May 2005; 28(5): 1107-12
17. Pearson J &Powers M.: Systematically Initiating Insulin. The Diabetes Educator 2006; 32; 19-28S
18. Barnett AH. A review of basal insulins. *Diabet Med*. 2003;20:873-885
19. Wright A, Burden AC et al. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). Diabetes Care. 2002;25:330-336

References

20. Triplitt C,How to Initiate, Titrate, and Intensify Insulin Treatment in Type 2 Diabetes US Pharm. 2007;32(10):10-16
21. CDA. *Can J Diabetes* 2013;37(suppl 1)