Diabetes Update: Incretin Agents in Diabetes-When to Use Them?

Spring Therapeutics Update 2011
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Disclosure

- I have no disclosures to declare

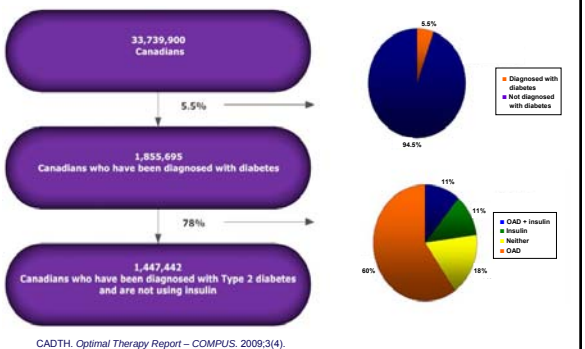
Learning Objectives

- Describe the similarities and differences btwn the 4 incretin agents available in Canada
- Explain when these medications would be used in a person with diabetes

Case

- 57 y.o person with type 2 diabetes on metformin 1g po bid and glyburide 10mg po bid now presents with an A1c of 8% and showing a continuous upward trend
- What would you recommend as the next step?

Canadians with Type 2 Diabetes Who Do Not Use Insulin



CADTH. *Optimal Therapy Report – COMPUS.* 2009;3(4).
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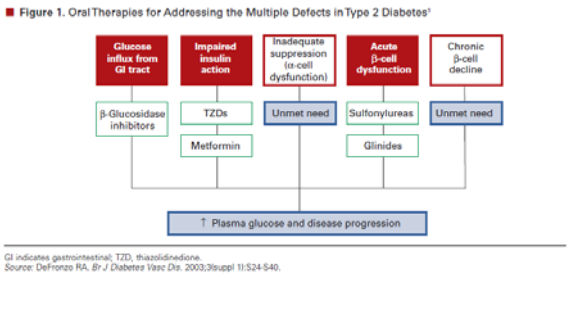
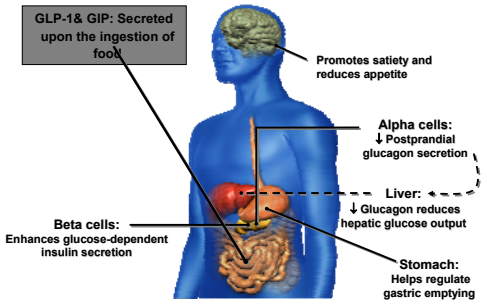


Incretin Agents

- Sitagliptin
- Saxagliptin
- Liraglutide
- Exenetide

Mechanism of Action



Data from Flint A, et al. *J Clin Invest.* 1998;101:515-520; Data from Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422
Data from Nauck MA, et al. *Diabetologia.* 1996;39:1546-1553; Data from Drucker DJ. *Diabetes.* 1998;47:159-169

Incretin Hormones

- GLP-1
  - Glucagon-like peptide
- GIP
  - Glucose dependent insulinotropic peptide
- Short half-life (<2 minutes)
  - DPP-4 enzyme hydrolyzes the incretins

Adapted from Drucker DJ. *Diabetes Care.* 2003;26:2929-2940

Type 2 Diabetes

- Resistant to GIP action
- Some resistance to GLP-1
  - GLP-1 is a protein
    - Therefore injectable

Sitagliptin
Saxagliptin

- DPP-4 inhibitors, incretin enhancers
- Increase concentration of GLP-1 and GIP
- Increase insulin release
- Decrease glucagon release
- Oral antihyperglycemic agents
- Weight neutral
- No hypoglycemia (rare)

Sitagliptin
Dose

- 100mg po daily with or without food
- 50mg po daily
  - eGFR 30-50ml/min
- 25mg po daily
  - eGFR <30 ml/min
- 79% excreted unchanged in the urine

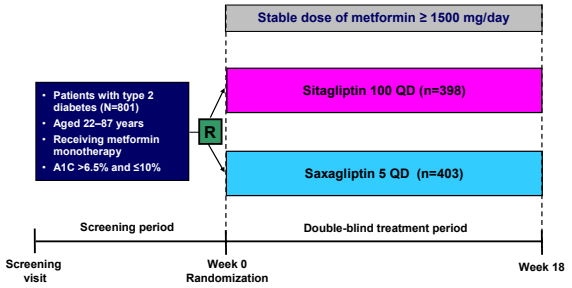
Saxagliptin - Dosing

- 24% excreted unchanged in urine
- eGFR > 50ml/min
  - 5mg po daily
- eGFR $\leq$ 50ml/min
  - 2.5mg po daily

Saxagliptin vs Sitagliptin?

- Saxagliptin
  - Associated with more interactions than sitagliptin
  - Metabolized via cytochrome P450 3A4/5
  - Be aware of drug interactions
    - Increased saxagliptin levels with diltiazem and ketoconazole?
    - Reduced saxagliptin levels with rifampin

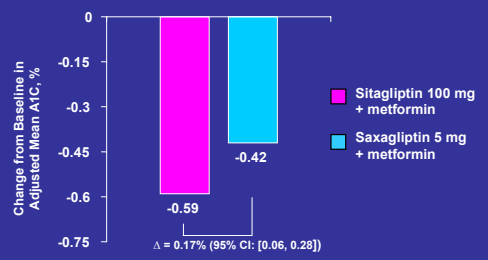
Saxagliptin vs Sitagliptin Noninferiority Study



- **Primary objective:** To evaluate the efficacy and safety of saxagliptin 5 mg vs sitagliptin 100 mg as add-on therapy to metformin in patients with type 2 diabetes who were inadequately controlled while receiving metformin alone.

Scheen AJ et al Diabetes Metab Res Rev 2010; 26: 540-549

A1c Change from Baseline



Non-inferiority of saxagliptin to sitagliptin confirmed in the full analysis set (upper limit of the 95% CI <0.3%)

Scheen AJ et al Diabetes Metab Res Rev 2010; 26: 540-549

Conclusions

- Saxagliptin is non-inferior to sitagliptin when added to metformin
- Clinically significant proportions of patients achieved target A1c without causing hypoglycemia or weight gain
- Both DPP-4 inhibitors were well tolerated with a similar incidence of adverse events

Scheen AJ et al Diabetes Metab Res Rev 2010; 26: 540-549

Liraglutide

- GLP-1 receptor agonist
  - Injectable-subcutaneously
  - Weight loss (2 kg)
  - No hypoglycemia (rare)
  - Store in fridge
  - When using then can keep at room temp x 1 month
  - Start with 0.6mg daily x 1 week to reduce GI symptoms then increase to 1.2mg sc daily
    - Can increase up to 1.8mg sc daily

Liraglutide - Renal Dosing

- Mild renal insufficiency
  - CrCL 50-80mL/min
  - No dose adjustment
- Moderate renal insufficiency
  - CrCL 30-50 mL/min
  - Limited experience
  - Product monograph:do not use
  - Clinical Pharmacology 2000:appears no dosage adjustment needed
- Severe renal insufficiency
  - CrCL <30 mL/min
  - Product monograph:do not use
  - Clinical Pharmacology 2000:appears no dosage adjustment needed

Liraglutide Canadian Monograph

- Causes dose dependent and treatment duration dependent thyroid c-cell tumours in rats and mice
- Not known if the same would occur in humans
- Contraindicated in people with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2

Suggested Monitoring

- Report mass in neck
- Dysphagea
- Dyspnea
- Persistent hoarseness
- Unknown if serum calcitonin monitoring or thyroid ultrasound may lower the risk
- May increase risk of unnecessary procedures due to low test specificity

Available as 3mL pen with 6mg/mL of Liraglutide
Prefilled disposable pen

Exenatide

- Incretin mimetic
- Similar to human hormone, GLP-1
  - Glucagon-like polypeptide-1
- NOC mid January
- Expected later in the spring

Dosage

- 5 mcg subcutaneously twice daily within 60 minutes of meal (before 2 main meals of the day, at least 6hrs apart)
- Do not administer after a meal
- After one month, can increase to 10 mcg twice daily
- May need to reduce dose of sulfonylurea by 50%

Do not use

- Creatinine clearance < 30 ml/min
- Severe GI disease
  - gastroparesis

Exenatide

- 2 fixed-dose prefilled pens
  - 5 µg per dose
  - 10 µg per dose

Adverse Effects

- Nausea
  - 44% exenatide vs 18% placebo
  - Withdrawal rate 7% vs 3% (placebo)
  - Tends to resolve as therapy is continued
  - Dose dependent
- Pancreatitis
  - Incidence
  - Delayed approval in Canada?
- Anti-exenatide antibody titers
  - Clinical significance unknown

Drug Interactions

- Slows gastric emptying
  - Take medications one hour before injecting exenatide
  - If medication is taken with food, take with snack

Exenatide LAR

- Once weekly
- Once monthly

Storage

- Refrigerate, protect from light
- Discard after 30 days

Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)

Summary

Background Unlike most antihyperglycaemic drugs, glucagon-like peptide-1 (GLP-1) receptor agonists have a glucose-dependent action and promote weight loss. We compared the efficacy and safety of liraglutide, a human GLP-1 analogue, with exenatide, an exendin-based GLP-1 receptor agonist.

Methods Adults with inadequately controlled type 2 diabetes on maximally tolerated doses of metformin, sulphonylurea, or both, were stratified by previous oral antidiabetic therapy and randomly assigned to receive additional liraglutide 1·8 mg once a day (n=233) or exenatide 10 μg twice a day (n=231) in a 26-week open-label, parallel-group, multinational (15 countries) study. The primary outcome was change in glycosylated haemoglobin (HbA_{1c}). Efficacy analyses were by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00318812.

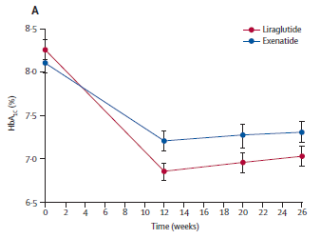
Findings Mean baseline HbA_{1c} for the study population was 8·2%. Liraglutide reduced mean HbA_{1c} significantly more than did exenatide [–1·12% [SE 0·08] vs –0·79% [0·08]; estimated treatment difference –0·33; 95% CI –0·47 to –0·18; p<0·0001] and more patients achieved a HbA_{1c} value of less than 7% (54% vs 43%, respectively; odds ratio 2·02; 95% CI 1·31 to 3·11; p=0·0015). Liraglutide reduced mean fasting plasma glucose more than did exenatide [–1·43 mmol/L [SE 0·20] vs –0·60 mmol/L [0·20]; estimated treatment difference –1·01 mmol/L; 95% CI –1·57 to –0·45; p<0·0001] but postprandial glucose control was less effective after breakfast and dinner. Both drugs promoted similar weight losses (liraglutide –3·24 kg vs exenatide –2·87 kg). Both drugs were well tolerated, but nausea was less persistent (estimated treatment rate ratio 0·648, p<0·0001) and minor hypoglycaemia less frequent with liraglutide than with exenatide (3·93 vs 2·40 events per patient per year; rate ratio 0·55; 95% CI 0·34 to 0·88; p=0·0131; 25·5% vs 33·6% had minor hypoglycaemia). Two patients taking both exenatide and a sulphonylurea had a major hypoglycaemic episode.

Interpretation Liraglutide once a day provided significantly greater improvements in glycaemic control than did exenatide twice a day, and was generally better tolerated. The results suggest that liraglutide might be a treatment option for type 2 diabetes, especially when weight loss and risk of hypoglycaemia are major considerations.

Funding Novo Nordisk A/S.

	Liraglutide 1·8 mg once a day (n=233)	Exenatide 10 μg twice a day (n=231)
Men	114 (49%)	127 (55%)
Age (years)	56·3 (9·8)	57·1 (10·8)
Race		
White	216 (93%)	210 (91%)
Body-mass index (kg/m²)	32·9 (5·5)	32·9 (5·7)
Duration of diabetes (years)	8·5 (6·2)	7·9 (5·9)
Fasting C-peptide (nmol/L)	1·25 (0·56)	1·26 (0·58)
Prestudy antidiabetic treatment		
Metformin and SU combination	145 (62%)	147 (64%)
SU alone	24 (10%)	21 (9%)
Metformin alone	64 (27%)	63 (27%)
HbA_{1c}	8·2% (1·0%)	8·1% (1·0%)

Primary Outcome: Change in A1c



-1.12% vs -0.79%
-0.33%;95% CI -0.47 to -0.18;
p<0.0001

Is this clinically significant?

Proportion of patients with an episode of nausea

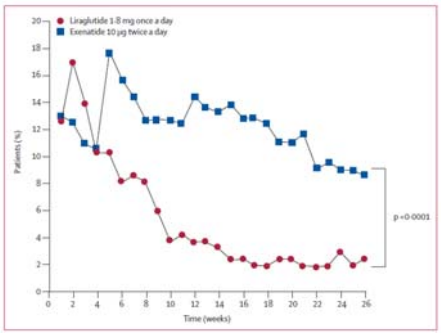


Table. Summary of Clinical Effects of Approved Incretin Therapies[23,24]

Drug	Approved Indication	Average A1C Reduction, %	Route of Administration	Dosing Frequency	Effect on Body Weight
GLP-1 receptor agonists					
Exenatide[27]	Adjunct to diet and exercise; + MET ± SU ± TZD	0.5%-1.0%	Subcutaneous injection	Twice daily	↓
Liraglutide[27]	Adjunct to diet and exercise; + MET ± SU ± TZD	0.5%-1.0%	Subcutaneous injection	Once daily	↓
DPP-4 inhibitors					
Sitagliptin[23]	Adjunct to diet and exercise; + MET and/or SU and/or TZD	0.5%-0.8%	Oral	Once daily	↔↑
Saxagliptin[24]	Adjunct to diet and exercise; + MET and/or SU and/or TZD	0.5%-0.8%	Oral	Once daily	↔↑

A1C indicates glycosylated hemoglobin; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione.

Am J Manag Care. 2010;16:S187-194

GLP-mimetics	DPP-IV inhibitors
Nausea, vomiting, diarrhoea, jittery, dizziness, headache, dyspepsia	Upper respiratory tract infection, nasopharyngitis, headache
Hypoglycaemia associated with coexisting sulphonylurea therapy	

DPP = dipeptidyl peptidase; GLP = glucagon-like peptide.

Clinical Medicine 2010 10;5:491-5

Benefits

Agent	A1c reduction (%)
Sulfonylureas	1-2
Metformin	1-2
Acarbose	0.5-0.8
Meglitinides*	1-1.5
TZDs	0.5-1.4
Incretins	0.5-1.0
Insulin	Regimen Dependent

*Repaglinide more effective than nateglinide

Diabetologia 2008;51:8-11
Can Fam Physician 2010;56:639-48

What about outcomes?

- **TECOS** (Trial Evaluating Cardiovascular Outcomes With Sitagliptin)
- **EXAMINE** (EXamination of CArdiovascular OutcoMes: AlogliptIN vs. Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome)..
- **SAVOR-TIMI 33** (Saxagliptin in Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus)..
- **EXSCEL** (Exenatide Study of Cardiovascular Event Lowering
- **LEADER** ((Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results).

Clinicaltrials.gov

Incretins in Clinical Trials

Inhibitor	Company
ABT-279,ABT-341	Abbott
ALS 2-0426	Alantos/Servier
BI 1356	Boehringer Ingelheim
Denagliptin	GSK
GRC8200	Glenmark
PSN-9301	OSI
PHX 1149	Phenomix
Saxagliptin	BMS/AstraXeneca
SSR-162369	Sanofi-Aventis
TS-021	Taisho
Alogliptin	Takeda
TA-6666	Tanabe

Cost

Class	Dosage	Cost
Biguanides		
metformin (Glucophage® ‡, generic†)	• 250 or 500 mg PO BID to max. 2.55 g/day (850 mg TID or 5 X 500 mg in divided doses)	$0.86/day (3x500 mg) G: $0.39/day (3x500 mg)
metformin extended-release (Glumetza®) ‡	• 1000 mg PO daily with evening meal, ↑ by 500 mg weekly to max 2000 mg/day	$1.73/day (1500 mg)
Insulin secretagogues – sulfonylureas		
gliclazide (Diamicron®, Diamicron® MR, generic)†	• 80-160 mg PO BID • gliclazide MR: 30-120 mg daily with breakfast	$0.80/day (2x80 mg) G: $0.60/day (2x80 mg) gliclazide MR: $0.15/day (1x30 mg)
glimepiride (Amaryl™, generic) ‡	• 1-8 mg PO daily	$0.67/day (1x1 mg) G: $0.52/day (1x1 mg)
glyburide (Diabeta®, Euglucon®, generic†)	• 5-10 mg PO daily or 2.5 mg BID	$0.25/day (1x5 mg) G: $0.07/day (1x5 mg)

http://www.bcguidelines.ca/gpac/pdf/diabetes_appendix_c.pdf

Cost

Insulin sensitizers (TZDs)		
pioglitazone (Actos®, generic)‡	• 15-45 mg PO daily	$3.37/ day (1x30 mg)
rosiglitazone (Avandia®)† §	• 2-8 mg PO daily or 4 mg BID (max daily dose 4 mg when combined with sulfonylurea)	$2.31/day (1x4 mg)
DPP-4 inhibitor (incretin enhancer)		
sitagliptin (Januvia™) ‡	• 100 mg PO daily	$3.00/day (1x100 mg)
saxagliptin (Onglyza™) ‡	• 5 mg PO daily	$2.84/day (1x5 mg)
Incretin mimetic (GLP-1)		
liraglutide (Victoza®) ‡	• 0.6 mg subcut once daily x 1 week then 1.2 mg subcut once daily, max 1.8 mg once daily.	$ 5.25 (1x1.2 mg) plus $0.40 per needle

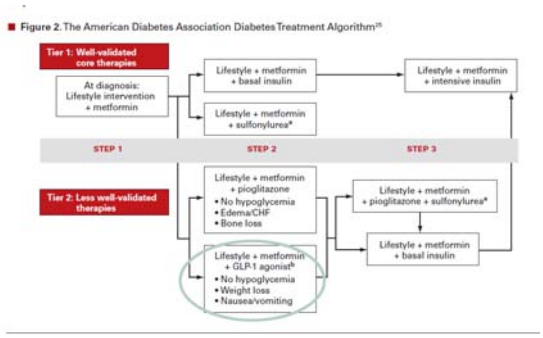
Exenatide approximately $7.00 per day – US pricing

http://www.bcguidelines.ca/gpac/pdf/diabetes_appendix_c.pdf

What do the Canadian Guidelines Recommend?

- Metformin first line
  - After diet and exercise
- Any of the other medications can be used 2nd line
  - Side effect profile
  - A1c reduction

www.diabetes.ca



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CADTH and BC Drug Benefit Council Recommendations

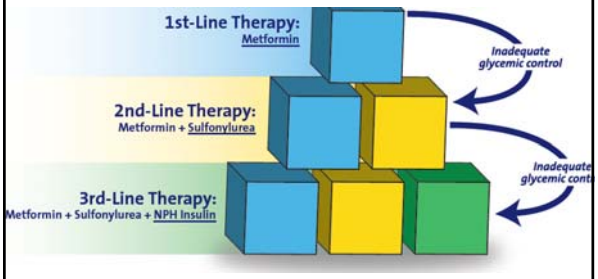
- CADTH = Canadian Agency for Drugs and Technologies in Health
- Reviewed evidence for optimal 2nd and 3rd line agents for Type 2 diabetes
  - Clinical evidence
  - Cost-effectiveness

http://www.health.gov.bc.ca/pharmacare/pdf/infosheet-on-diabetes-therapy.pdf

Which Drugs Did They Include in Their Review?

- Sulfonylureas
- Insulin
- Pioglitazone and Rosiglitazone
- Saxagliptin, Sitagliptin, Liraglutide
- Nateglinide, Repaglinide
- Acarbose

http://www.health.gov.bc.ca/pharmacare/pdf/infosheet-on-diabetes-therapy.pdf



If insulin is not an option then sitagliptin can be considered as 3rd line

www.cadth.ca/t2dm

Why Sulfonylureas as 2nd Line?

- All drugs reviewed achieved statistically significant A1c reductions
  - 0.6-1.0%
- Hypoglycemia
  - Severe hypoglycemia:rare
- Most cost effective
- Long term safety data available

http://www.health.gov.bc.ca/pharmacare/pdf/infosheet-on-diabetes-therapy.pdf

Why Insulin as 3rd Line?

- All drugs reviewed achieved statistically significant A1c reductions except for meglitinides and acarbose
  - 0.9-1.2%
- Hypoglycemia was more common
  - Severe hypoglycemia:rare
- Most cost-effective 3rd line drug
- Long term safety known

http://www.health.gov.bc.ca/pharmacare/pdf/infosheet-on-diabetes-therapy.pdf

What about rosiglitazone and pioglitazone?

- Rosiglitazone now requires pt consent
  - No longer covered by PharmaCare
- If NPH insulin is not an option then pioglitazone is available via special authority

http://www.health.gov.bc.ca/pharmacare/pdf/infosheet-on-diabetes-therapy.pdf

What about incretins?

- If NPH insulin is not an option then sitagliptin is available via special authority
- Saxagliptin and Liraglutide are not benefits at this time

http://www.health.gov.bc.ca/pharmacare/pdf/infosheet-on-diabetes-therapy.pdf

Is that drug covered? Why or why not?

- http://www.health.gov.bc.ca/pharmacare/decision.html


Ministry of Health

BC PharmaCare Drug Coverage Decisions

This section of our website gives you information about:

- how drug coverage decisions are made
- how you can provide input into those decisions
- why and when a coverage decision was made
- whether PharmaCare covers a specific drug
- how manufacturers can request that a drug be considered for PharmaCare coverage

Select a link below for more information.

How drug coverage decisions are made	Drug Review Process - Overview Drug Review Process - Detailed	About the Drug Benefit Council
Making your voice heard	NEW! Input to Drug Reviews for Patients, Caregivers and Patient Advocacy Groups	
Finding out what decision was made and why	Results of PharmaCare Drug Reviews	Drug Decision Summaries
Is your drug covered by PharmaCare?	NEW! PharmaCare Drug Benefit Search	
Requesting that a drug be	Drug Submission Requirements - Patented Drugs	

Case

- 57 y.o person with type 2 diabetes on metformin 1g po bid and glyburide 10mg po bid now presents with an A1c of 8% and showing a continuous upward trend
- What would you recommend as the next step?