


**Insulin preparations:
Which types for which patients?
Examining the Evidence**

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Name	Do you have any affiliations (financial or otherwise) with a commercial organization that may have a direct or indirect connection to the content of the workshop?
Dr. Marshall Dahl	<p>Eli Lilly – Olanzapine – 2 workshops in 2006 (\$3,000)</p> <p>GlaxoSmithKline – arms length grant in 2004 for a diabetes study in coronary artery patients (\$10,000)</p> <p>Sanofi-aventis – Amaryl – funding/honorarium for 1 lecture in 2003</p> <p>Eli Lilly – diabetes care – travel to a diabetes course in December 2001</p> <p>Merck Frosst – Sitagliptin – funding/honorarium for 1 lecture in 2007</p> <p>Eli Lilly – insulin therapies – funding/honorarium for 1 lecture in 2007</p> <p>Novo Nordisk – management of glycemic emergencies – funding/honorarium for 1 lecture in 2009</p>



**Insulin preparations:
Which types for which patients?**

Please remember to...

- ✓ Sign the attendance form (include your email)
- ✓ Fill out an evaluation form

Learning objectives

Upon completion of this workshop the participant will:

- Understand the evidence base supporting the use of human insulin and insulin analogues in the treatment of diabetes
- Identify the appropriate use of insulin preparations in:
 - The general population with diabetes
 - Special cases where insulin analogues should be considered.

Outline

Context

- Diabetes in Canada
- Physiology and pathophysiology of diabetes
- Options for insulin therapy

The evidence base for optimal therapy

- Scientific process
- Conclusions and recommendations

Where did the evidence come from?

Canadian Agency for Drugs and Technologies in Health (CADTH)

CADTH is an independent, not-for-profit agency funded by Canadian federal, provincial, and territorial governments to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision makers.



Diabetes in Canada (Types 1 and 2 combined)

Prevalence

- In 2005-2006, approximately 1.9 million were diagnosed with diabetes
- One in 17 people had been diagnosed with diabetes
- The prevalence rate for both males and females was 5.9%

Incidence

- In 2005-2006, 199,471 individuals were newly diagnosed with diabetes - 6.4 per 1,000 overall

PHAC. Report from the National Diabetes Surveillance System: Diabetes in Canada, 2008



Diabetes in Canada

Disease burden

- Diabetes shortens life expectancy for all ages.
 - For example, 25 to 39-year old people with diabetes had an approximate nine year reduction in life expectancy in 2005-2006.

PHAC. Report from the National Diabetes Surveillance System: Diabetes in Canada, 2008



Physiology of insulin

Basal insulin secretion

- Background low-level continuous secretion
- Prevents keto-acidosis

Variable biphasic meal-stimulated secretion

- first phase rapid
- second phase lasts longer

Insulin-receptor binding stimulates glucose uptake by target tissues

Eaton, et al. *J Clin Endocrinol Metab* 1990;71:1508-1518.
Polonsky, et al. *J Clin Invest* 1988;81:442-448.
Kruszynska, et al. *Diabetologia* 1987;30:16-21.
Polonsky, et al. *J Clin Invest* 1986;77:98-105.
Wakdhaus, et al. *Diabetologia* 1979;17:221-227.

Insulin secretion in a person without diabetes

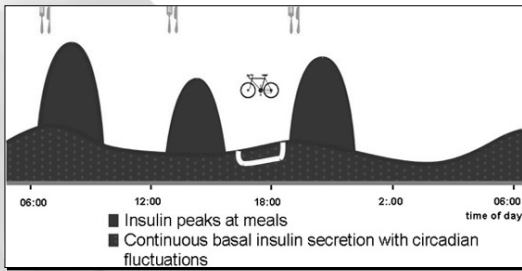


Image used with permission from: *Why use pump therapy?* Warwick (UK): Advanced Therapeutics (UK) Ltd, 2009.

Diabetes types: Insulin requirements

Type 1: autoimmune. Complete insulin deficiency

- Always requires insulin treatment

Type 2: insulin resistance and progressive loss of insulin secretory ability

- Initial pharmacologic treatment with oral agents for most patients
- Patients may require insulin at a later date

Pregnancy

- Gestational Diabetes: similar to temporary type 2 diabetes; insulin therapy initiated if glycemic targets not achieved after 2 weeks from nutrition therapy alone
- Women with type 1 and type 2 diabetes have additional management issues when pregnant

WHO. *Definition, diagnosis and classification of diabetes mellitus and its complications*, 1999. CDA. *Can J Diabetes* 2008;32(suppl 1):S201.

Human insulin

- Genetically-engineered production from bacteria
- Different types have different pharmacokinetics due to solubility of diluent which affects absorption
- Brand names: “Humulin®, Novolin ®”
- “Prandial” or “Bolus” or Short-acting
 - “R”, “Regular”, “Toronto”
 - Onset 30 minutes, peak 2-3 hours, duration 6.5 hours

CDA. *Can J Diabetes* 2008;32(suppl 1):S201.
CADTH. *Optimal Therapy Report - COMPLUS* 2008;2(7).



Human insulin (cont'd)

- “Basal” or Intermediate-acting
 - “N”, “NPH”
 - Onset 1-3 hours, peak 5-8 hours, duration up to 18 hours
- Mixture of these two types:
 - 30/70 (30%R and 70%N), 50/50

CDA. *Can J Diabetes* 2008;32(suppl 1):S201.
CADTH. *Optimal Therapy Report - COMPLUS* 2008;2(7).



Insulin analogues

Modified structures to change pharmacokinetics

- Switching sequences of amino acids (lispro, aspart)
- Addition of amino acids (glargine) or fatty acid moiety (detemir)

Rapid-acting insulin analogues: (“Bolus” insulins)

- Lispro (Humalog®) and aspart (NovoRapid®)
- Onset 10-15 min, peak 1-2 hours, duration 3-5 hours

CDA. *Can J Diabetes* 2008;32(suppl 1):S201.
CADTH. *Optimal Therapy Report - COMPLUS* 2008;2(7).



Approximate unit costs of bolus insulins* (cont'd)

Vial, 1x 10 mL, 100 units/mL:

- NovoRapid®=\$26.90
- Humalog ®=\$25.80
- Humulin ® R=\$18.90
- Novolin ® ge Toronto=\$19.40

Cartridge, 5x3 mL, 100 units/mL:

- NovoRapid ®=\$53.70
- Humalog ®=\$51.60
- Humulin ®R=\$37.95
- Novolin ® Toronto=\$38.10

*Costs are current as of December, 2008 and may vary between regions and over time.

**Studying the evidence:
COMPUS Expert Review Committee**

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ON	Dr. L. Dolovich	Pharmacist/Health Economist
ON	Dr. M. Evans	Family Physician/Practice Support
ON	Panos Petrides	Public Member
NS	Dr. M. Allen	Family Physician/Health Education
NS	Cathy MacNutt	Public Member


**Scientific process:
Selection of clinical outcomes**

- **Surrogate outcomes:**
 - A1C
 - Fasting plasma glucose
 - Two hour post-prandial glucose
- **Short-term complications:**
 - Severe hypoglycemia
 - Nocturnal hypoglycemia
 - Overall hypoglycemia

Scientific process:
Selection of clinical outcomes (cont'd)

- Long-term complications/mortality
- Other surrogates: weight gain, BMI, blood pressure, LDL, % of patients A1C<7.0%
- Health-related quality of life and patient satisfaction
- Health care resource use

CADTH. Optimal Therapy Report - COMPUS 2008:2(1).
 CADTH. Optimal Therapy Report - COMPUS 2008:2(2).




Scientific process: Systematic review

Systematic Review

- Search of world literature for studies of relevance
- Previous systematic reviews and meta-analyses
- Primary studies: Randomized-controlled (RCT), non-randomized controlled, and observational studies all considered
- Two independent researchers then rate studies for inclusion (e.g., excluded if target outcomes not obtainable)
- Quality of evidence depends on study design, conduct and analysis
- For this project:
 - 123 articles were included in the systematic review

CADTH. Optimal Therapy Report - COMPUS 2008:2(1).
 CADTH. Optimal Therapy Report - COMPUS 2008:2(2).



Considering the evidence

Studies first analyzed for evidence of clinical benefit and harm

- Safety, effectiveness and clinically-important differences (if any)


Results then analyzed on the basis of cost for clinical benefit

Recommendations formulated

- based on efficacy, safety and pharmacoeconomic data
- "GRADE" process ranks the quality of evidence and the strength of each recommendation

Feedback sought from advocacy groups and industry

CADTH. Optimal Therapy Report - COMPUS 2008:2(7).



Information gaps

Human insulins and insulin analogues:

- Most studies look at surrogate outcomes (lab tests, clinical measurements such as blood pressure, weight) and short-term complications (hypoglycemia)

Virtually no studies on important long-term outcomes yet: diabetes related mortality, and microvascular and macrovascular disease

Example of scientific process

In patients with type 2 diabetes on oral antidiabetes drugs who also require a basal insulin:

Are there advantages for either NPH or glargine?

Glargine vs. NPH in patients with type 2 diabetes on oral antidiabetes drugs

Clinical Outcomes:

- A1C
- Fasting plasma glucose
- Severe hypoglycemia
- Nocturnal hypoglycemia
- Overall hypoglycemia
- Long-term complications/mortality
- Surrogates: weight gain, BMI, blood pressure, LDL, % of patients A1C < 7.0
- Health-related quality of life and patient satisfaction

Cost-effectiveness

Glargine vs. NPH in patients with type 2 diabetes on oral antidiabetes drugs (cont'd)

Health-related quality of life and patient satisfaction

- Mean improvement score in treatment satisfaction significantly favoured glargine over NPH:
 - 1 RCT, N=481, moderate quality study

Cost-effectiveness

- How is this determined?

CADTH. *Optimal Therapy Report - COMPUS 2008:2(1)*.
Eliashewitz, et al. *Arch Med Res* 2006;37(4):495-501.



Cost-effectiveness

Difference in treatment cost between strategies:

- \$4,945 more expensive for glargine
- Difference in Quality-Adjusted Life Years (QALY): A commonly used measure of health and life-span
 - incremental benefit of 0.008 QALY with glargine

Incremental cost-utility analysis

- Cost of glargine – cost of NPH/QALYs glargine-QALYs NPH
- There is no concrete cost-effectiveness threshold used in Canada
 - Published cost-effectiveness thresholds have ranged from \$20,000/QALY - \$100,000/QALY
- Glargine vs. NPH: \$642,994/QALY gained

CADTH. *Optimal Therapy Report - COMPUS 2008:2(1)*. Laupacis, et al. *CMAJ* 1992;146(4):473-81.
Culyer, et al. *J Health Serv Res Policy* 2007;12(1):56-8. McCabe, et al. *Pharmacoeconomics* 2008;26(9):733-44.
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Glargine vs. NPH in patients with type 2 diabetes on oral antidiabetes drugs

Recommendation:

- NPH be used in preference to glargine in most adults with type 2 diabetes taking oral antidiabetes drugs who require a basal insulin

Primary consideration:

- The incremental cost of glargine over insulin NPH outweighs its modest clinical benefit in this situation

Strength of recommendation: "Strong"

Quality of clinical evidence: "Moderate"

CADTH. *Optimal Therapy Report - COMPUS 2008:2(1)*.



Glargine vs. NPH: Type 1 diabetes (adults)*

Outcome	RCTs (Total sample size)	Effect estimate (95% CI)
A1C	8 (N=2,406)	-0.12 (-0.25 to -0.01) reduction with glargine
Severe hypoglycemia (relative risk)	6 (N=2,113)	0.81 (0.49 to 1.36)
Nocturnal Hypoglycemia (relative risk)	5 (N=1,943)	0.97 (0.87 to 1.09)
Overall Hypoglycemia (relative risk)	5 (N=1,893)	1.02 (0.97 to 1.07)
Weight	3 (N=1,138)	Favoured glargine
Long-term complications/mortality		Retinopathy no difference
HRQoL and Patient satisfaction	1 (N=517)	No difference reported for HRQoL. Patient satisfaction favoured glargine.
Cost effectiveness		\$87,932 per QALY gained

A1C=Glycosylated hemoglobin; CI=Confidence interval; HRQoL=Health-related quality of life; QALY=Quality-adjusted life year; RCT=Randomized controlled trial.

*Common pre-meal bolus insulin in both treatment study groups

CADTH. Optimal Therapy Report - COMPUS 2008;2(7).



Detemir vs. NPH: Type 1 diabetes (adults)*

Outcome	RCTs (Total sample size)	Effect estimate (95% CI)
A1C	7 (N=2,558)	-0.06 (-0.13, 0.02) No statistical difference
Severe hypoglycemia (relative risk)	7 (N=2,442)	Favoured detemir
Nocturnal Hypoglycemia (relative risk)	6 (N=2,311)	Favoured detemir
Overall Hypoglycemia (relative risk)	6 (N=2,110)	No difference
Weight	6 (N=2,302)	Favoured detemir
Long-term complications/all cause mortality		No difference
Patient satisfaction	No studies	Not applicable
Cost effectiveness		\$387,729 per QALY gained

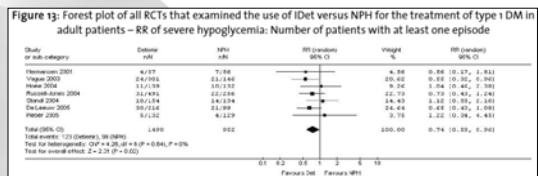
A1C=Glycosylated hemoglobin; CI=Confidence interval; QALY=Quality-adjusted life year; RCT=Randomized controlled trial.

*Common pre-meal bolus insulin in both treatment study groups

CADTH. Optimal Therapy Report - COMPUS 2008;2(7).



Forest plot of the relative risk of severe hypoglycemia (number of patients with at least one episode) from all RCTs examining Detemir vs. NPH in adult patients with type 1 diabetes



DM=Diabetes mellitus; CI=Confidence interval; IDet=Insulin detemir; NPH=Neutral protamine Hagedorn; RCT=Randomized controlled trial; RR=Relative risk

CADTH. Optimal Therapy Report - COMPUS 2008;2(1).



Long-acting insulin analogues and hypoglycemia

Some comparative studies demonstrated a reduced risk/incidence of hypoglycemia with long-acting insulin analogues vs. NPH

- Not observed consistently across studies
- Hypoglycemia not consistently defined

Adults with type 1 diabetes with prior severe recurrent hypoglycemia actually excluded from seven of nine trials comparing detemir with NPH

Long-acting insulin analogues: Key message

In patients with type 1 diabetes or type 2 diabetes requiring basal insulin, insulin NPH should be considered first.

Although the evidence is limited and inconsistent, patients experiencing significant hypoglycemia while using insulin NPH may benefit from long-acting insulin analogues.

Bolus insulin therapy (lispro or aspart) vs. regular insulin

Type 1 diabetes: (Children, adolescents, adults and pregnancy)

- No clinically significant differences in A1C, however there was a marginal benefit
- Hypoglycemia: marginal benefits in some studies for pump users and adults and adolescents on multiple doses
- Significant increase patient satisfaction
- \$673,041 per QALY gained is only for type 1 adults using MDI (lispro vs. human insulin);
- \$104,598 per QALY gained is for type 1 adults using MDI (aspart vs. human insulin)

Key message: Bolus insulin type 1 diabetes

In patients with type 1 diabetes, either regular human insulin or rapid-acting insulin analogues can be considered as first-line therapy (except in adolescent patients).

In adolescent patients with type 1 diabetes, rapid-acting insulin analogues may be considered as first-line therapy.

Bolus insulin type 1 diabetes special considerations

Regular human insulin may be preferred when

- Affordability is an important consideration

Consider rapid-acting insulin analogues when:

- Flexibility of administration with meals is of primary importance
- Significant hypoglycemia is experienced while using regular human insulin, or in cases where hypoglycemia is a major concern

Rapid-acting insulin analogues are preferred for adolescents using multiple daily injections

- Evidence for lispro
- A better fit for the unpredictable patterns of dietary intake and activity

Bolus insulin type 2 diabetes Lispro vs. regular insulin

Outcome	RCTs (Total sample size)	Effect estimate (95% CI)
A1C	11 (N=3,093)	No significant difference
Severe hypoglycemia (relative risk)	2 (N=1,622)	No significant difference
Nocturnal Hypoglycemia (relative risk)	1 (N=178)	No significant difference
Overall Hypoglycemia (relative risk)	3 (N=384)	No significant difference
Weight	3 (N=1,682)	No significant difference
All cause mortality	1 (N=80)	No significant difference
Patient satisfaction	1 (N=885)	No significant difference
Cost-effectiveness		\$130,865 per QALY gained

A1C=Glycosylated hemoglobin; CI=Confidence interval; QALY=Quality-adjusted life year; RCT=Randomized controlled trial.

Key message: Bolus insulin

In patients with type 2 diabetes requiring bolus insulin, regular human insulin may be considered first.

- Although the evidence is limited and inconsistent, patients who are experiencing significant hypoglycemia while taking human insulin may benefit from rapid-acting insulin analogues.

Cases where insulin analogues should be considered

Adolescents with type 1 diabetes

- Insulin lispro is recommended as first line bolus insulin

Although the evidence is limited and inconsistent, patients with type 2 diabetes who are experiencing significant hypoglycemia while taking human insulin may benefit from rapid-acting insulin analogues

Other patient factors favoring analogue consideration:

- Flexibility of dose and meal timing for rapid-acting insulin analogues
- Increased patient satisfaction in some studies

Pregnancy

Type 1 diabetes in pregnancy

- Bolus insulin: either regular insulin or rapid-acting insulin analogues
- Basal insulin:
 - Long-acting insulin analogues not studied

Gestational diabetes

- Bolus insulin: either regular insulin or rapid-acting insulin analogues (e.g., insulin aspart)
- Basal insulin
 - Long-acting insulin analogues not studied

Learning objectives

Understand the evidence-base which supports the use of human insulins and insulin analogues in the treatment of diabetes

- Systematic review of world literature
- Pooled meta-analysis of peer-reviewed trials
- Recommendations based on clinical evidence with pharmacoeconomic analysis added afterwards

Learning objectives (cont'd)

Identify the appropriate use of insulin preparations in:

- The general population with diabetes
 - First-line agents for bolus insulin:
 - Adults with type 1 diabetes: regular human insulin or rapid-acting insulin analogues
 - Adolescents with type 1 diabetes, insulin lispro or rapid-acting insulin analogues suggested over regular human insulin
 - Type 1 diabetes in pregnancy and gestational diabetes: regular human insulin or rapid-acting insulin analogues
 - Type 2 diabetes: regular human insulin
- First-line agents for basal insulin:
 - Type 1 and type 2 diabetes: NPH insulin

Learning objectives (cont'd)

Identify special cases where insulin analogues should be considered:

- Adolescents with type 1 diabetes: lispro for bolus
- Hypoglycemia (severe episodes) in any patient: both rapid- and long-acting insulin analogues
- Patient convenience/meal flexibility: rapid-acting insulin analogue
- Patient preference

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