

Insulin Analogues and SMBG

Messages from Dalhousie CME

Academic Detailing

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Disclosure statements

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Pam and Jill provide drug evaluation support to the Nova Scotia Department of Health

Outline

- Clinical Questions
- Background information
- Insulin Analogue Therapy
 - Evidence
 - COMPUS and CDA recommendations
- Blood Glucose Test Strips
 - Evidence
 - COMPUS and CDA recommendations

Three questions

1. Do the insulin analogues provide any clinically important reduction in A1C levels compared to human insulins?
2. Do the insulin analogues provide any clinically important reduction in hypoglycemia compared to human insulins?
3. Who should be self-monitoring their blood glucose? How often should they monitor?

Academic Detailing Program

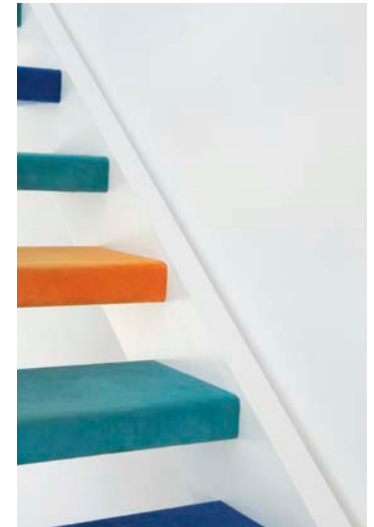
- Managed by Dalhousie CME and funded by the Department of Health.
- Trained health care professionals visit practitioners individually to provide evidence-based CME on a particular topic in brief educational sessions.
- Material developed with the assistance of an advisory board consisting of four family physicians and topic-specific specialists from across NS.
- Academic detailing is available to all Nova Scotia family physicians and interested specialists, but participation is completely voluntary and confidential.
- To date, over 65% of Nova Scotia family physicians have participated in one or more AD programs.

COMPUS

- Canadian Optimal Medication Prescribing and Utilization Service
 - program of CADTH
 - Pan-Canadian service funded by Health Canada
 - In partnership with the Federal, Provincial, and Territorial Health Ministries, COMPUS identifies and promotes optimal drug therapy
- COMPUS Expert Review Committee
 - 12 member panel
 - Including endocrinologists, pharmacists, family physicians

Considering the evidence

- Step 1: Evidence of clinical benefit and harm
 - Safety, efficacy, and clinically-important differences
- Step 2: Economic evidence
 - Cost-effectiveness
- Step 3: Recommendations formulated
“GRADE” process
 - quality of evidence: low, moderate, high
 - strength of each recommendation: weak or strong
- Step 4: Feedback from stakeholders such as advocacy groups and industry



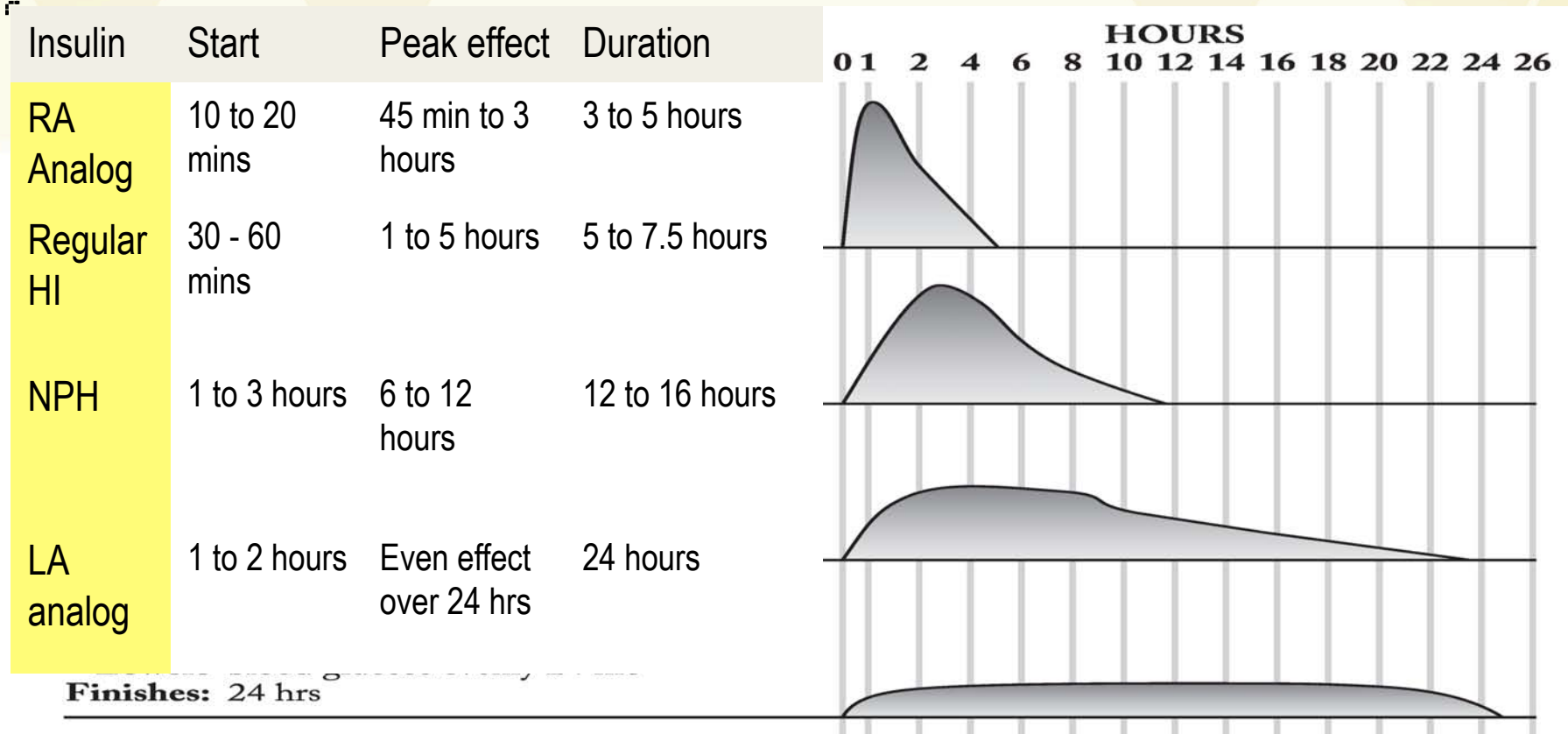
Two recent COMPUS topics

- Insulin Analogue Therapy
- Blood Glucose Test Strips

We will consider:

- A. What is the evidence for their use?
- B. What are the recommendations for their use?

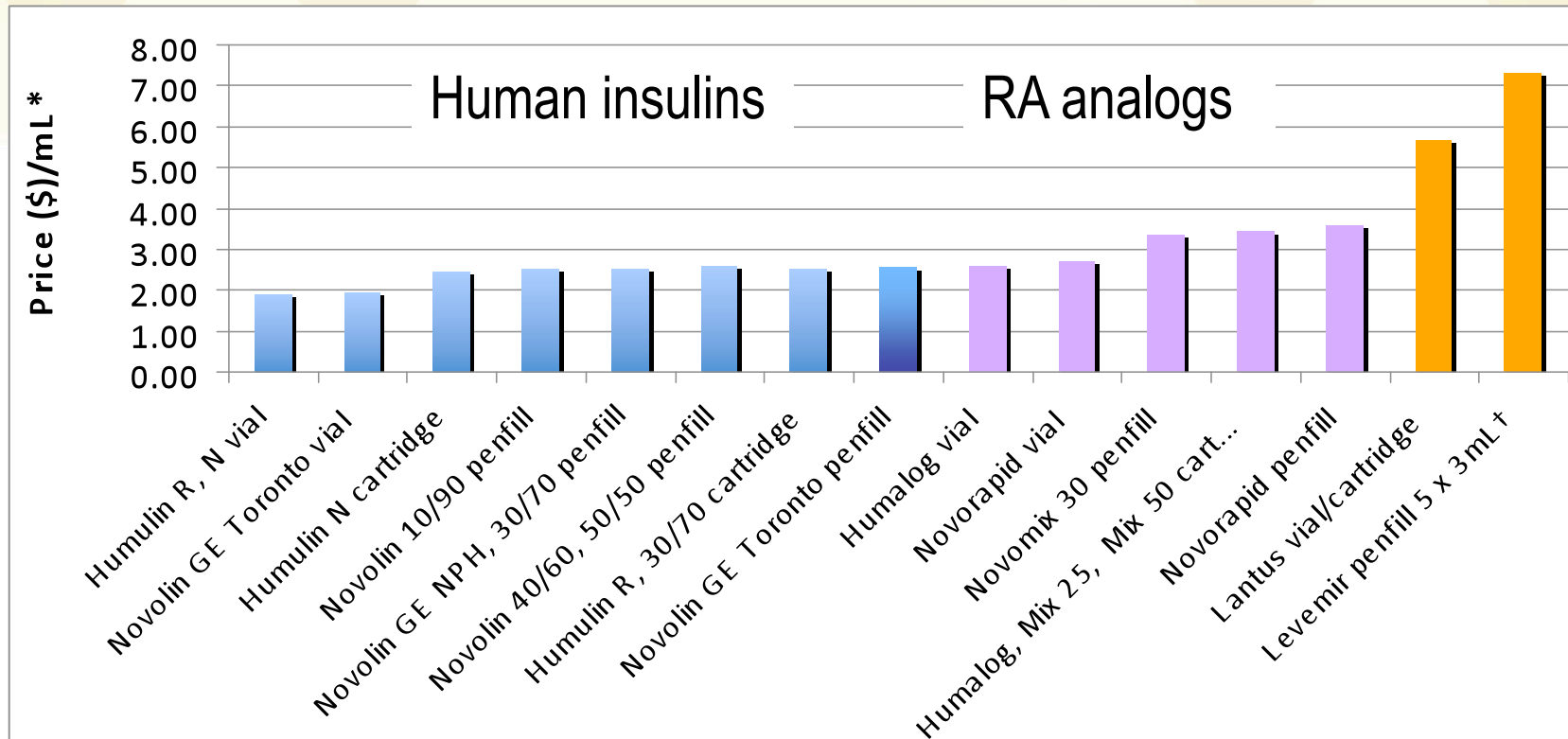
Time-Action Profile



American Diabetes Association. Used with permission. Developed by University of Michigan Health System from original material - American Diabetes Association, October 2008.

Insulin price comparison

LA analogs



■ Human insulin
 ■ Rapid-acting insulin analogs
 ■ Long-acting insulin analogs

*Ontario Drug Benefits Formulary/Comparative Drug Index [database on the Internet]; 2008 Dec 3.

† D. Groleau, NovoNordisk Canada, Mississauga, ON: personal communication, 2008 Dec 9.

Outcomes

Critically important

Most frequently reported

- Glycemia
 - A1c, Fasting plasma glucose, 2 hour PC glucose
- Hypoglycemia
 - Severe, nocturnal, overall
- Clinical
 - Mortality, CHD, stroke, PVD, retinopathy, nephropathy, neuropathy
- Metabolic
 - Body weight, BMI
- Quality of life
 - Satisfaction with care, quality of life

Question 1 Insulin Analogues

Do the insulin analogues provide any **clinically important reduction** in **A1C levels** compared to human insulins?

NO



Statistical vs clinical significance

A1c clinically significant difference

= 0.7 to 1.0 percentage point

A1C: summary of evidence

- Meta-analyses indicate **no clinically significant difference** in **A1C** levels between insulin analogues and human insulin in any population.
 - Adults or children with type 1 diabetes or
 - Adults with type 2 diabetes (children with type 2 diabetes have not been studied)
- No statistically significant difference was greater than 0.3 percentage points.

Question 2 Insulin Analogues

Do the insulin analogues provide any **clinically important reduction** in **hypoglycemia** compared to human insulins?

???

Hypoglycemia as a clinical trial outcome

- Different Categories
 - Overall vs. Severe vs. Nocturnal
- Different ways to report each outcome
 - Risk ratios and / or Rate ratios
- Limitations of individual studies
 - Lack of clear definitions for hypoglycemia
 - Studies were unblinded
 - patients with history of recurrent severe hypoglycemia were EXCLUDED (mostly for detemir)

Benefit of Analogues in Hypoglycemia

- Overall
 - Benefit from the insulin analogues in hypoglycemia was **INCONSISTENT** in clinical trials
- One outcome with most consistent benefit
 - Nocturnal hypoglycemia in two populations
 1. **Rapid-acting** analogues in adults and adolescents with **type 1** diabetes
 2. **Long-acting** analogues in adults with **type 2** diabetes.

There were **no consistent differences** between the analogues and human insulin in **overall or severe hypoglycaemia**

r

Population

Rapid-acting analogues in adults and adolescents with **type 1** diabetes

Long-acting analogues in adults with **type 2** diabetes.

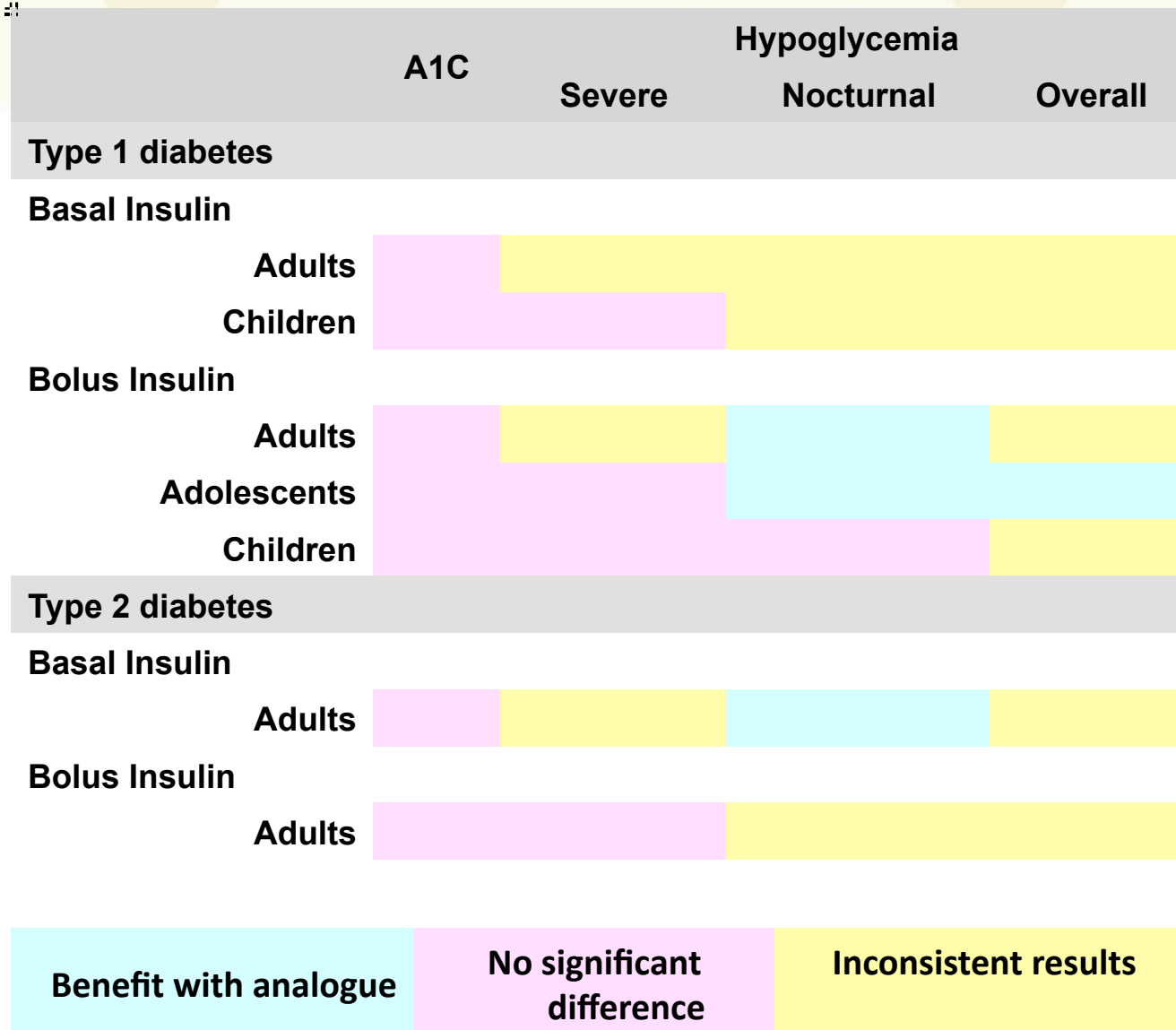
Nocturnal Hypoglycemia

Relative Rate Reduction \approx 40%
Risk was **not** reported

Absolute Risk Reduction
 \approx 6 to 14%
NNT \approx 6 to 13

There are **limitations** of nocturnal hypoglycemia as a clinical trial outcome

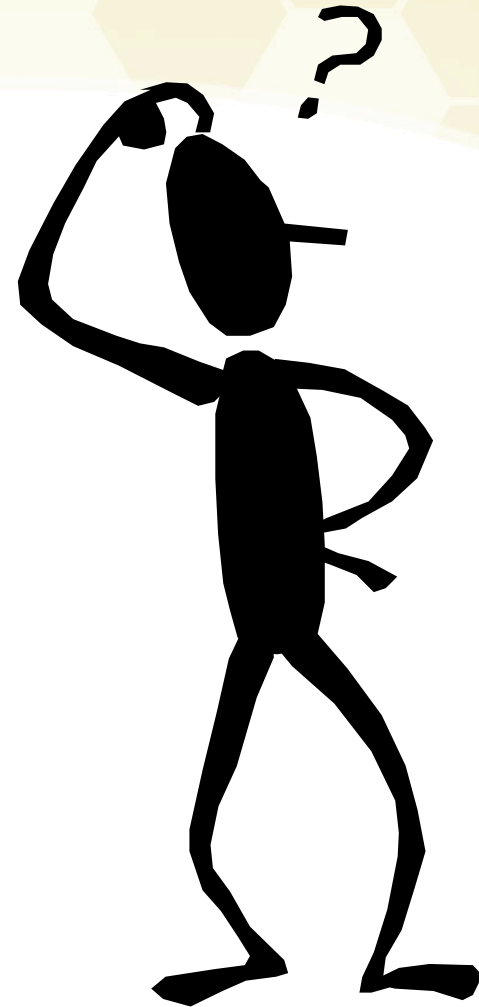
Insulin analogues vs human insulins: Summary of COMPUS findings



For a patient with type 1 diabetes which basal (background) insulin would you choose?

Analogue or NPH?

What about a patient with type 2 diabetes?

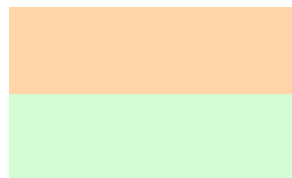


COMPUS recommendations for human insulins and insulin analogues

Type of insulin	Type 1 diabetes			Type 2 diabetes
	Adults	Adolescents	Children	Adults
Basal	NPH	NPH	NPH	NPH
Bolus	Reg HI or IA	IA	Reg HI or IA	Reg HI

Strong recommendation

Weak recommendation



Comparison to CDA 2008 Recommendations

- COMPUS and CDA recommendations are similar
 - CDA: “consider”, “may be considered”
 - COMPUS: “suggested”
- Potential differences to highlight
 - The use of rapid-acting analogues in type 2 diabetes
 - Wording of recommendations for Basal insulins

CDA Recommendations 2008

COMPUS Recommendations 2009

Type 2 adults

Rapid/
short
acting

Use rapid-acting insulin analogues instead of short-acting insulin to lower postprandial blood glucose levels.^a

Grade B, Level 2

Regular human insulin is **suggested** over the rapid acting analogues.^b

Weak recommendation; low quality evidence

Long
acting

When basal insulin is added to antihyperglycemic agents, long-acting analogues **may be considered** instead of NPH to reduce the risk of nocturnal and symptomatic hypoglycemia.

Grade A, Level 1A

NPH is **recommended over** long acting insulin analogues.

Strong recommendation; low / moderate quality evidence

IMPORTANT: COMPUS recommendations consider cost-effectiveness

Summary

1. BASAL or long-acting analogs
 - NPH recommended first in type 1 and type 2 diabetes
2. BOLUS or rapid-acting analogs
 - Type 1: Regular insulin OR rapid-acting analogs recommended as first line except for adolescents
 - Adolescents: Rapid-acting analog suggested as first line over regular human insulin
 - Type 2: Regular human insulin suggested as first line over rapid-acting analogs
3. Reasons for considering analogues
 - Convenience or episodes of hypoglycemia
4. No preference for one analog over another

Nova Scotia Formulary Coverage

Insulin

Regular
Benefit

Exception
Status

Non-Benefit

Regular



Lispro
Aspart

children
 ≤ 18 yrs old

adults
 ≥ 19 years old

Glulisine

NPH



Glargine

Determir



ACADEMIC DETAILING MESSAGES

SELF MONITORING OF BLOOD GLUCOSE (SMBG)

Pam McLean-Veysey





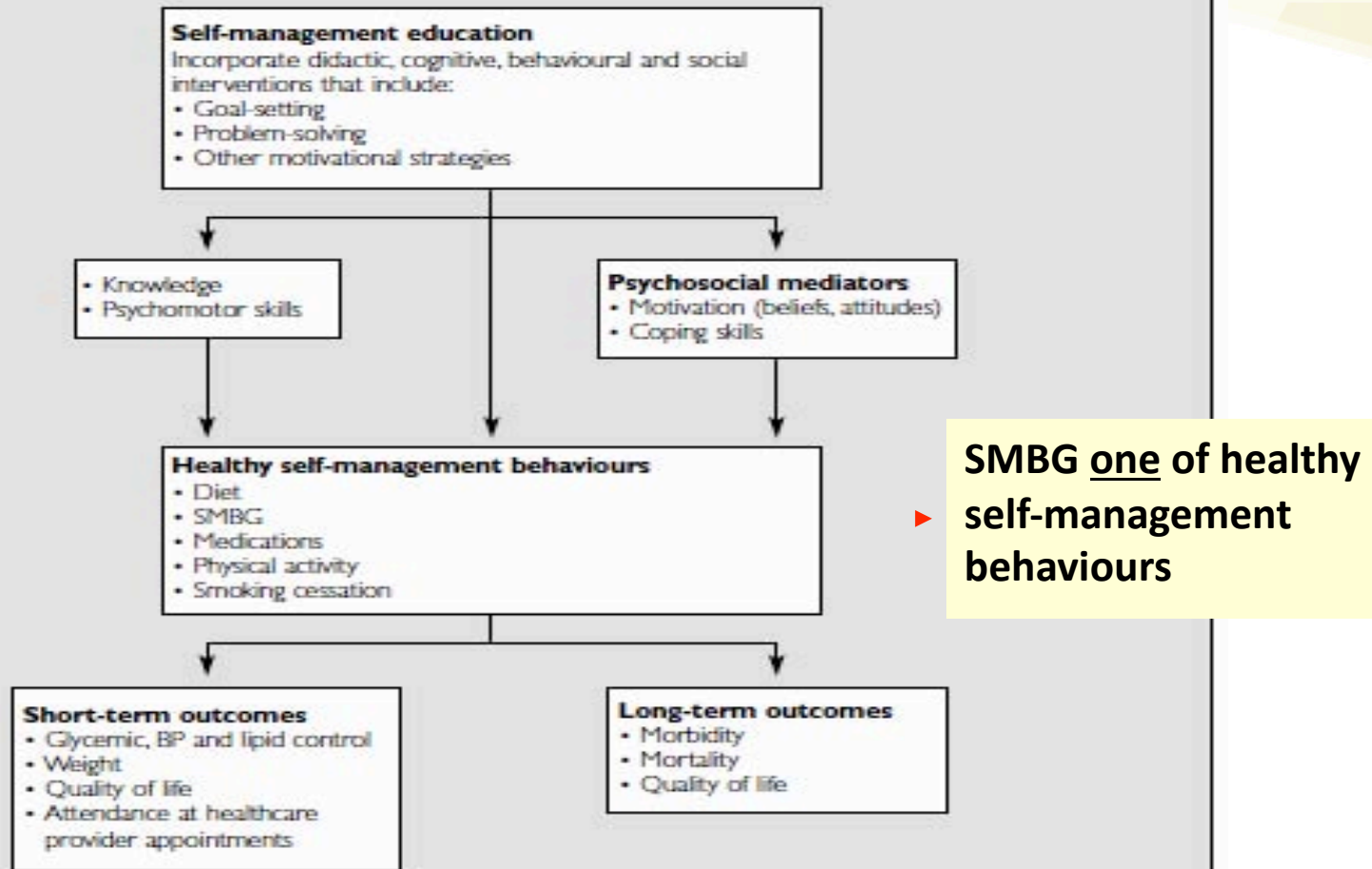
“The first commandment is: Thou shalt not shoot the messenger.”

WHY SMBG?

- The main reasons for self-monitoring of blood glucose are to
 - Improve adherence to glycemic targets
 - Reduce episodes of hypoglycemia
 - Monitor hyperglycemia in acute situations
- SMBG should be used when linked to specific patient actions such as
 - Prevention or treatment of hypoglycemia
 - Self-directed medication dosage adjustment

Role of SMBG in Self Management

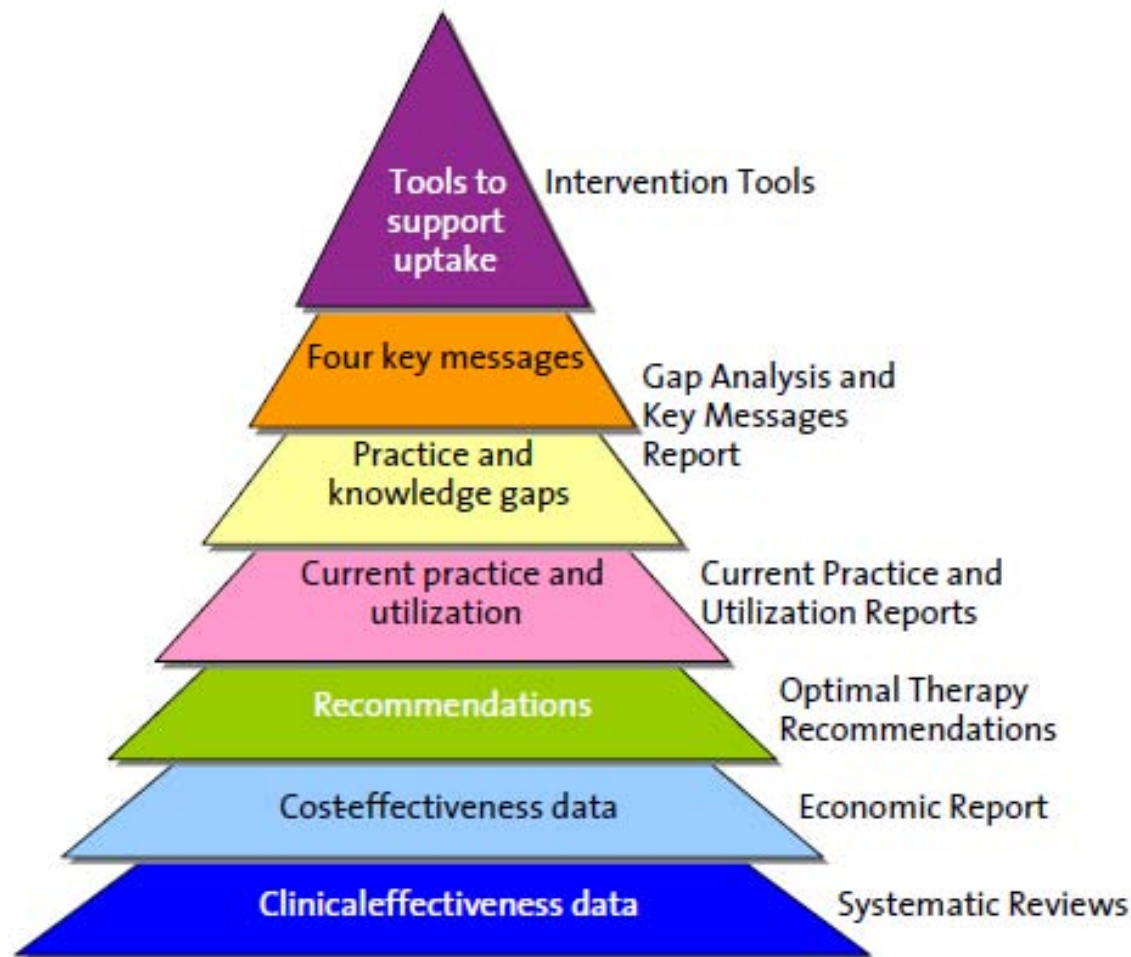
Figure 1. Process of teaching people to manage their diabetes (adapted from 28)



BP = blood pressure
SMBG = self-monitoring of blood glucose

Ref: CDA 2008

AD messages based on COMPUS material



<http://www.cadth.ca/index.php/en/compus/blood-glucose>

COMPUS recommendations vary depending on whether the patient is using insulin.

Generally, it is recommended that

- Patients ***using insulin*** perform SMBG
- Most adults ***not using insulin*** do **not** require routine SMBG

COMPUS Key Messages

Insulin Users

(with or without oral antihyperglycemic agents)



Type 1 or type 2 diabetes using basal-bolus insulin:

- SMBG should be individualized to guide adjustments in insulin therapy to achieve optimal blood glucose control.

Adults with type 2 diabetes using basal insulin

- Testing of up to 14 times per week should be sufficient for most patients at most times.

Basal Insulin

Why up to 14 tests per week?

- COMPUS rated evidence as low quality and this is a **weak** recommendation.
 - It is based on standards of practice and a cost-effectiveness analysis
 - Testing 14 times per week may be cost-effective if it leads to a decrease in A1C of 0.5% to 0.75%.
 - Approximately \$50,000 - \$75,000 /QALY (ICUR)
- CDA 2008 recommendation is to test at least once a day, at variable times in this population.

More frequent testing?

Based on clinical experience and accepted standards of practice, some conditions may require more frequent testing.

For example:

- Multiple daily insulin injections (i.e., three or more per day)
- History of hypoglycemia
- Occupation where hypoglycemia poses safety concerns
 - testing is mandated by an employer (e.g., pilots, air-traffic controllers, critical positions in railways)
- Private and commercial drivers
 - jurisdictional regulations concerning SMBG, hypoglycemia, and operation of motor vehicles.
- Newly initiated on insulin
- Experiencing acute illness
- Undergoing changes in insulin dose/regimen or significant changes in routine.
- Poorly controlled or unstable blood glucose levels
- Pregnant or planning a pregnancy

COMPUS Key Message SMBG

Oral antihyperglycemic Drugs

Routine use of SMBG is **not recommended** for **most adults** with type 2 diabetes using oral antihyperglycemic drugs.

- Strong recommendation; low to moderate level of evidence
- **Periodic testing in selected patients, for example**
 - Unstable glucose levels
 - acute illness, unplanned physical activity
 - pharmacotherapy changes
 - risk of hypoglycemia with insulin secretagogues (e.g., Glyburide, gliclazide, etc.)
 - Pregnant or planning a pregnancy

Efficacy Outcome Measure

A1C

Type 1

- Study which reported the largest reduction in the trials reviewed by COMPUS. Karter 2001
 - Mean difference in A1C reduction:
 - 0.78% (95% CI: 0.55 to 1.01) in favor of testing ≥ 3 times per day vs. once per day.
 - Very low quality retrospective cohort study.

Type 2 (oral agents or no pharmacotherapy)

- 7 RCTs (n= 2270)
 - Mean difference in A1C reduction
 - 0.25% (95% CI: 0.15 to 0.36) for SMBG vs. no monitoring
 - **Statistically** significant but **not clinically** significant
 - Similar results in patients using sulfonylureas

Efficacy Outcomes

Hypoglycemic Events/Well being

Type 2 not requiring insulin (SMBG vs no SMBG)

3 RCTs (n=1752)

- **Increase** in at least one **overall** hypoglycemic event with SMBG.
 - Risk 15% vs. 7.6%, relative risk increase 99%, absolute risk increase 7.4%;
 - Number needed to test 13 (95% CI: 7 to 36).
 - Most **mild or asymptomatic**
 - Increase **COULD BE** due to detecting hypoglycemia with monitoring.
 - No affect on **severe or nocturnal** hypoglycemia (studies were not powered to detect such differences.)

2 RCTs (n=794) patients found a **decrease** in the **rate** of hypoglycemic events:

- Rate ratio 0.73 (95% CI: 0.55 to 0.98).

- SMBG was not associated with improvements in well-being or satisfaction with treatment and showed increased levels of depression and poorer quality of life.

COMPUS Economic Analysis

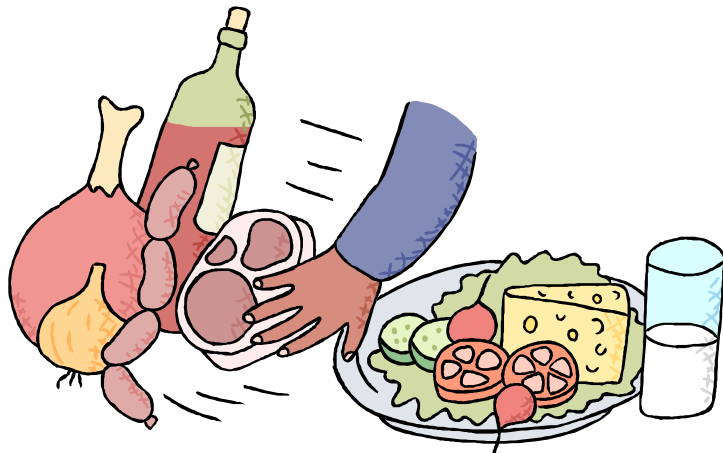
Non-insulin Users

- Daily SMBG in all patients with type 2 diabetes not using insulin does not represent an efficient use of finite healthcare resources
- Daily use is associated with an incremental cost of
 - \$113,643 per QALY gained.
- Periodic use (e.g., one to two test strips per week) may be cost-effective.
- Reducing the price of test strips would significantly improve cost-effectiveness.

COMPUS Key Message

Diabetes controlled by diet

Most adults with type 2 diabetes controlled by diet alone should not require **routine SMBG**



Efficacy Outcome

A1C

Type 2 using no antihyperglycemic drugs

- 1 RCT (n=124)
 - Mean difference in A1C
 - 0.05% (95% CI -0.33 to 0.23)
 - Not statistically significant

Similarities and differences in recommendations

CDA SMBG Recommendations 2008

COMPUS SMBG Recommendations 2009

Type 1 adults and children

Recommended as an essential part of diabetes self management *Grade A, Level 1*

- at **least 3 times** per day *Grade C, Level 3*

include both pre- and postprandial tests

Grade C, Level 3

The optimal daily frequency should be **individualized** for adults and children with type 1 diabetes

Strong recommendation; low-quality evidence

Type 2 adults using insulin

Using Insulin

SMBG recommended as an essential part of diabetes self-management **Grade C, Level 3**

- at **least 3 times** per day *Grade C, Level 3*

- include both pre- and postprandial tests

Grade C, Level 3

Frequency should be **individualized** for most adults with type 2 diabetes using insulin with or without oral antidiabetes drugs

Strong recommendation; low quality evidence

Suggested **maximum** average weekly frequency of SMBG for **most** adults with type 2 diabetes using [basal] insulin with or without oral antidiabetes drugs

Type 2 Once daily Insulin Plus oral agents

Once-daily insulin plus oral antihyperglycemic Agents

- test at **least once** a day at variable times

Grade D, Consensus.

- **14 tests per week.**

Weak recommendation; low quality evidence

Similarities and differences in recommendations

CDA SMBG
Recommendations 2008

COMPUS SMBG
Recommendations 2009

Type 2 Controlling with diet alone or oral agents

- The frequency of SMBG should be **individualized** depending on glycemic control and type of therapy.

- Should include both **pre- and postprandial** measurements

Grade D, Consensus.

- Routine use of blood glucose test strips for SMBG is

- **not recommended** for most adults with type 2 diabetes using oral antidiabetes drugs or diet alone

Strong recommendation; low / moderate quality evidence

Financial Considerations

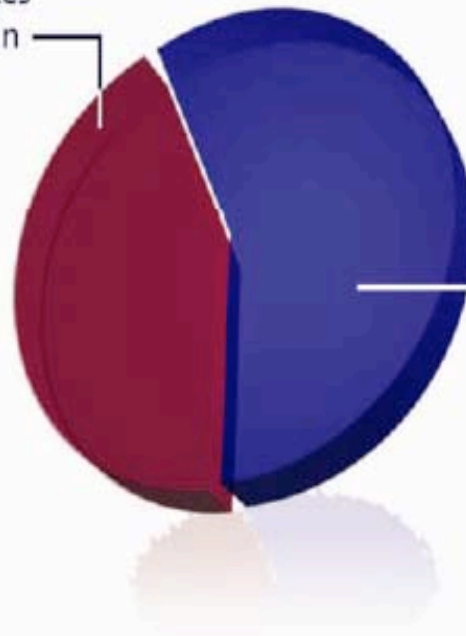
- In 2008 spending within the NS Pharmacare program was:
 - Diabetes medications \$8,532,000
 - Glucose test strips \$8,522,200
- > \$4,000,000 for patients where routine testing is not recommended (oral antidiabetes drugs or no drugs).
 - \$870,000 in those on no drugs.

COMPUS QUICK REFERENCE PRESCRIBING AID

Total Spending in Canadian Publicly and Privately Funded Drug Plans on Blood Glucose Test Strips Exceeded

\$330 Million* in 2006

Patients with diabetes
who are using insulin
\$144,000,000



*This estimate is based on data from eight publicly funded drug plans in Canada (British Columbia, Manitoba, Newfoundland and Labrador, Non-Insured Health Benefits, Nova Scotia, Ontario, Quebec, and Saskatchewan) plus data from 67% of privately funded drug plans that submitted data to Brogan Inc. Some patients in the dataset could not be classified by province or territory, therefore, the estimate is understated.

Patients with
diabetes who are
not using insulin
\$188,000,000

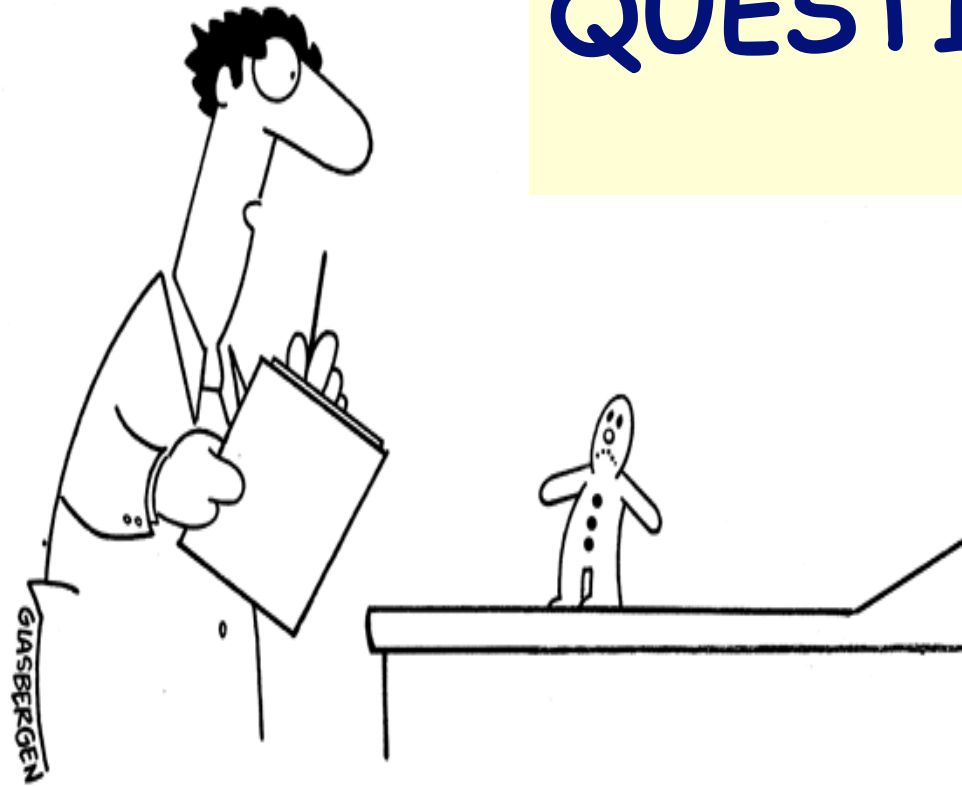
Summary

- There is little evidence to guide recommendations on SMBG
 - Evidence is of low/moderate quality, mostly observational studies.
- Recommendations are primarily based on consensus and usual care.
- COMPUS includes cost considerations in recommendations.
- Consider opportunity costs
 - resources can be used elsewhere.



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QUESTIONS?



"Your blood sugar is too high."