Institute of Health Economics: Alberta STE Report

Insulin pump therapy for type 1 diabetes

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IHE INSTITUTE OF HEALTH ECONOMICS ALBERTA CANADA

Institute of Health Economics

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Alberta STE Report

Insulin pump therapy for type 1 diabetes

Alberta STE Report: Policy-driven Health Technology Assessment reports that include an analysis of the social and system demographics, technological effectiveness and economic implications of a health technology. The reports are written under contract with the Alberta Health Technology Decision Process and contextualized for use in Alberta.

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EXECUTIVE SUMMARY

The Alberta Health and Wellness' Executive Committee accepted the Alberta Health Technology Decision Program's Advisory Committee's recommendation to undertake a STE analysis of insulin delivery systems. The purpose of this report is to address the following questions of interest:

- What is the potential role of insulin pump therapy (IPT) in the intensive treatment of Albertans with type 1 diabetes mellitus (T1DM) compared to multiple daily injections (MDI)?
- What subpopulation(s) would benefit from IPT compared with MDI (syringe and pen)?
- What are the established criteria for initiating IPT?
- What are the economic considerations for IPT compared with MDI?

T1DM, characterized by high blood glucose levels that require lifelong insulin therapy, can cause short- and long-term complications in different organs such as the heart, eyes, kidneys, and blood vessels. It may cause neuro-cognitive dysfunction and behavioural changes in children. In pregnant women high glucose levels are associated with increased risk of fetal congenital malformation, peri-natal mortality, obstetric complications, and neonatal morbidity.

Although T1DM usually accounts for only a minority of the total burden of diabetes in a population (approximately 10%), it is the most predominant form of the disease in younger age groups in most developed countries. It can develop at any age but usually appears in childhood or adolescence. Males and females tend to be equally vulnerable.

Over 240,000 Canadians live with T1DM. In 2007 the estimated number of prevalent cases of T1DM among Canadian youth (0 to 14 years) was 8400. The incidence rate for this age group was estimated at 21.7 per 100,000 cases in 2007. The estimated incidence rate increases with age from 14.7 for 0- to 4-year-olds, to 24.0 for 5- to 9-year-olds, and 26.3 for 10- to 14-year-olds.

Intensive management of T1DM delivered by MDI is the accepted standard of care for achieving and maintaining near-normal blood glucose in order to reduce the risk of complications. Despite recent advances in intensive insulin therapy, fear of inducing hypoglycemia remains a major barrier in achieving optimal glycemic control safely in all age groups. Guidelines for intensive insulin therapy of T1DM recommend an individualized, intensive insulin regimen using either MDI or IPT. IPT is usually considered after MDI has been tried but has failed to optimize glycemic control safely.

An insulin pump is a complex computerized electronic device used for continuous subcutaneous insulin infusion. IPT consists of a basal-bolus injection; i.e., continuous infusion of low-dose rapid-acting insulin analogues (such as insulin lispro or insulin aspart) and pre-meal bolus injections of rapid-acting insulin analogues. There are three main insulin pump manufacturers whose pumps are available on the Canadian market with licence approval from Health Canada: Animas Canada, Disetronic Medical Systems, and Medtronic of Canada.

Both MDI and IPT are available in Alberta and, according to Alberta experts, most individuals with T1DM are MDI users (approximately 12% of youth and 13% of adults are IPT users). The key components of a high-quality IPT service are identifying individuals with T1DM suitable for IPT, ensuring appropriate composition of the specialist team (physician with a special interest in IPT, a diabetes nurse specialist, and a dietitian), and monitoring and supporting IPT users.

The evidence reviewed on IPT in pregnancy included studies published more than 10 years ago (from 1986 to 1993). The lack of new RCTs makes it impossible to examine the safety and efficacy of newer generations of insulin pumps and insulin analogues in this subpopulation.

The evidence reviewed indicates that IPT is as safe as MDI in terms of frequency of severe hypoglycemia (abnormally low blood glucose levels) episodes and diabetic ketoacidosis (abnormally high blood glucose levels) for adult patients, preschool children, children and adolescents, and pregnant women. Management by both IPT and MDI resulted in significant reductions in glycosylated hemoglobin (A1C) from baseline levels. However, when compared to MDI, individuals using IPT had slightly lower A1C levels. This finding was similar across all age groups. Patient satisfaction, although not a direct measure of QoL, was found to be higher with IPT.

The studies were generally of short durations (less than 2 years) of follow-up. Long-term outcomes such as changes in the secondary complications of diabetes, which include retinopathy and cardiovascular, renal, or neurologic diseases, remain to be determined.

The currently available evidence failed to demonstrate the clinical superiority of IPT over MDI. There were no clinically significant differences in terms of the frequency of severe hypoglycemia episodes and the magnitudes of A1C reduction in all age groups, including pregnant women. In particular, there was a lack of studies that included patients with a history of recurrent severe hypoglycemia or hypoglycemia unawareness using MDI, which is one of the primary indications for switching to IPT. The research evidence was insufficient to establish appropriate criteria for initiating IPT and to identify appropriate patient subgroups that would benefit clinically from IPT.

There was limited evidence in the economic research literature on the cost-effectiveness of IPT compared to MDI. Only one study provided evidence on the cost-effectiveness of IPT compared to MDI in a highly select group of adults with severe hypoglycemia. It found that the cost per additional quality-adjusted life year gained was GBP 11,461 for IPT users. The authors concluded that IPT was cost-effective when targeted at those who had more than two severe hypoglycemic events per year and required hospital inpatient treatment at least once every 8 months for hypoglycemia.

The analysis of administrative health data indicates that in 2007 the health service utilization costs in Alberta for patients with T1DM, including associated secondary complications, on hospital, outpatient, and physician resources is estimated to be CAD 8247, CAD 715, and CAD 149 per patient respectively. The budget impact of switching eligible patients from MDI to IPT is estimated at CAD 14.57 million over 3 years. The cost per IPT user per year is approximately CAD 4700 in the first year and CAD 4600 in the subsequent years. When excluding consumables and considering only the costs associated with the insulin pump, the cost per patient per year is estimated to be CAD 5360 in the first year and CAD 5250 in the subsequent years, a total budget impact of CAD 16.63 million over 3 years. Adults account for 80% of the costs, followed by adolescents at 15%, pregnant women at 3%, and children at 2%.

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ABBREVIATIONS

A1C – glycosylated/glycated hemoglobin

ACHORD – Alliance for Canadian Health Outcomes Research in Diabetes

ADA – American Diabetes Association

ADDQoL – Audit of Diabetes-Dependent Quality of Life

AETMIS – Agence d'évaluation des technologies et des modes d'intervention en santé

ADSS – Alberta Diabetes Surveillance System

AUD – Australian dollar

BG – blood glucose

BMI – body mass index

CCHS – Canadian Community Health Survey

CDA – Canadian Diabetes Association

CEA – cost-effectiveness analysis

CGM – continuous glucose monitoring

CI – confidence interval

CIHI – Canadian Institute for Health Information

CRD – Centre for Reviews and Dissemination

CSII – continuous subcutaneous insulin infusion

CUA – cost-utility analysis

DCCT – Diabetes Control and Complications Trial

DHCC – Diabetes, Hypertension & Cholesterol Centre

DKA – diabetes ketoacidosis

dl – deciliter

DM – diabetes mellitus

DMS – data management software

DQoL – Diabetes Quality of Life

EDIC – Epidemiology of Diabetes Interventions and Complications

F – female

FDA – Food and Drug Administration

ft – feet

g – gram

GBP – Great Britain pound

GDM – gestational diabetes mellitus

h – hour

HrQoL – health-related quality of life

HTA – health technology assessment

ICER – incremental cost-effectiveness ratio

IDDM – insulin-dependent diabetes mellitus

IDF – International Diabetes Federation

INPUT – INsulin PUmp Therapy (British advocacy group that promotes the use of the pump)

IPT – insulin pump therapy

IPWG – Insulin Pumps Working Group

ITT – intention to treat

L – liter

LE – life expectancy

M – male

MBG – mean blood glucose

MDI – multiple daily injection

mg – miligram

min – minute

NA – data not available

NHS – National Health System

NICE – National Institute for Clinical Excellence

NIDDM – non–insulin-dependent diabetes mellitus

NPH – neutral protamine Hagedorn (a basal insulin)

NR – not reported

NS – difference not significant

OGTT – oral glucose tolerance test

OR – odds ratio

PC – personal computer

PDA – personal digital assistant

PUMP – Pump Management for Professionals (group of professionals in Great Britain)

P-Y – person-years

QoL – quality of life

QALY – quality-adjusted life year

RCTs – randomized controlled trials

RR – relative risk

RT – real time

SH – severe hypoglycemia

SMBG – self-monitoring of blood glucose

SR – systematic review

ss – statistically significant

T1DM – type 1 diabetes mellitus

T2DM – type 2 diabetes mellitus

TDD – total daily dose

TEAE – treatment-emergent adserse event

U – unit

UK – The United Kingdom

UKPDS – UK Prospective Diabetes Survey

USA – United States

USD – United States dollars

WHO – World Health Organization

WMD – weighted mean difference

yr – year

GLOSSARY/DICTIONARY

The glossary terms listed below were obtained and adapted from the following sources:

www.childrenwithdiabetes.com

www.diabetes.ca

www.diabetes.org

www.diabetes.niddk.nih.gov

www.disetronic-ca.com/dstrnc_ca

www.jdrf.ca

www.jdrf.org

www.medical-dictionary.com

www.medicaldictionaryweb.com

Acidosis – too much acid in the body. For a person with diabetes, this can lead to diabetic ketoacidosis.

Antibodies – proteins made by the body to protect itself from "foreign" substances such as bacteria or viruses.

Autoimmune disease – disorder of the body's immune system in which the immune system mistakenly attacks and destroys body tissue that it believes to be foreign.

Autoimmune thyroid disease – an autoimmune disease that occurs when the body's immune system attacks its own thyroid cells, reducing or even destroying thyroid function.

Beta cell – a cell in the pancreas that makes insulin. Beta cells are located in the islets of the pancreas (called the islets of Langerhans).

Blood glucose level – the amount or concentration of glucose in a given amount of blood. In Canada blood glucose is measured in millimoles of glucose per litre of blood (mmol/L); the normal range before meals is 4.0 to 6.0 mmol/L, whereas the normal range 2 hours after a meal is 5.0 to 8.0 mmol/L.

Bolus – an extra amount of insulin taken to cover an expected rise in blood glucose, often related to a meal or snack.

Brittle diabetes – a term used when a person's blood glucose level moves often from low to high and from high to low; though not a distinct form of diabetes and now considered an outmoded term, it refers to diabetes that is very difficult to control.

Calorie – a unit representing the energy provided by food; the sources of calories in a diet are carbohydrate, protein, alcohol, and fat.

Carbohydrate – one of the main nutrients in food and one of the main sources of calories. Sources of carbohydrates include sugars naturally found in honey, fruits, vegetables, and milk; refined sugars such as table sugar and sugars added to candies, jams, and soft drinks; and starches such as grains, rice, potatoes, corn, and legumes. All forms of carbohydrate are broken down into glucose during digestion.

Carbohydrate counting – a method of meal planning for people with diabetes based on counting the number of grams of carbohydrate in food.

Celiac disease – an autoimmune disease characterized by sensitivity to gluten, a protein found in wheat.

Continuous glucose monitor – a blood glucose monitor with a small sensor that is inserted under the skin; this monitor automatically checks blood glucose levels every few minutes.

Conventional insulin therapy – consists of one or two daily insulin injections.

Conventional therapy – a system of diabetes management practiced by most people with diabetes. The system consists of one or two insulin injections each day, daily self-monitoring of blood glucose levels, and a standard program of nutrition (meal planning) and exercise along with regular visits to healthcare providers. The main objective in this form of treatment is to avoid very high and very low blood glucose levels. It is also called "standard therapy."

Dawn phenomenon – an increase in the blood sugar in the morning, possibly caused by the release of counterregulatory hormones such as cortisol, glucagon, and epinephrine, all of which can signal the liver to release glucose.

Diabetes – a disease in which the body either cannot produce insulin or cannot properly use the insulin it produces. This leads to high levels of glucose in the blood, which can damage organs, blood vessels, and nerves.

Diabetes Control and Complications Trial (DCCT) – a multicentre randomized controlled trial conducted between 1983 and 1993 that enrolled 1441 patients with type 1 diabetes from 29 centres and compared the effects of intensive insulin therapy (MDI or IPT) and conventional insulin therapy (defined as one or two daily insulin injections) on the long-term complications of diabetes.

Diabetic ketoacidosis (DKA) – an acute and severe complication of diabetes in which extremely high blood glucose levels, along with a severe lack of insulin, result in the breakdown of body fat for energy and an accumulation of ketones (acids) in the blood and urine.

Diabetic retinopathy – a disease in which the small blood vessels (capillaries) in the back of the eye (retina) bleed or form new vessels.

Fasting blood glucose test – a test of a person's blood glucose level after the person has not eaten for 8 to 12 hours (usually overnight).

Glucagon – a hormone produced by the alpha cells in the pancreas (in areas called the islets of Langerhans) that causes an increase in the blood glucose level.

Glycemic variability – the fluctuation in blood glucose levels throughout the day and is typically characterized by postprandial hyperglycemic spikes.

Glucose – a simple sugar found in the blood that serves as the body's main source of energy, also known as dextrose.

Glycosuria – the presence of high levels of glucose in the urine, which can indicate abnormally high blood glucose levels.

Glycosylated hemoglobin (A1C) – a measure of the blood glucose levels over the previous 120 days. Also called glycated hemoglobin.

Honeymoon phase – the period of time after the diagnosis of type 1 diabetes when the dose of insulin may need to be reduced due to remaining or recovered insulin secretion from the pancreas; this period can last weeks, months, or years.

Human insulin – a synthetic form of insulin created in the 1990s using recombinant-DNA technology.

Hyperglycemia – higher-than-normal blood glucose levels. Fasting hyperglycemia is blood glucose above a desirable level after a person has fasted for at least 8 hours; postprandial hyperglycemia is blood glucose above a desirable level 1 to 2 hours after a person has eaten.

Hypoglycemia – a condition that occurs when one's blood glucose level is lower than normal; it is also called an insulin reaction.

Hypoglycemia unawareness – a state in which a person does not feel or recognize the symptoms of hypoglycemia.

Implantable insulin pump – a small pump placed inside the body to deliver insulin in response to remote-control commands from the user.

Incidence – a measure of how often a disease occurs. It is the number of new cases of a disease among a certain group of people for a certain period of time.

Inhaled insulin – a treatment for taking insulin using a portable device that allows a person to breathe in insulin.

Insulin – a hormone produced by the beta cells of the pancreas that controls the amount of glucose in the blood.

Insulin analogue – insulin that is made chemically as a modification of human insulin.

Insulin antagonist – something that opposes or fights the action of insulin; glucagon is an antagonist of insulin.

Insulin-induced hypertrophy – small lumps that form under the skin when a person repeatedly injects a needle in the same spot.

Insulin pen – an injection device the size of a pen that includes a needle and holds a vial of insulin.

Insulin pump – a portable, battery-operated device that delivers a specific amount of insulin through a small needle inserted under the skin. It can be programmed to deliver constant doses of insulin throughout the day, deliver extra insulin as required, or both. It is also called continuous subcutaneous insulin infusion (CSII).

Intensive insulin therapy – therapy that consists of three or more daily insulin injections or treatment with an insulin pump.

Intensive management – a treatment program for diabetes that uses intensive insulin therapy with the goal of imitating the function of a healthy pancreas by taking several doses of insulin throughout the day.

Islet cells (islets) – groups of cells located in the pancreas that produce hormones that help the body break down and use food.

Islet cell transplantation – a procedure currently employed in human clinical trials that involves taking beta (islet) cells from a donor pancreas and putting them into a person whose pancreas has stopped producing insulin.

Intermediate-acting insulin – a type of insulin that starts to lower blood glucose within 1 to 2 hours after injection and has its strongest effect 6 to 12 hours after injection, depending on the type used.

Jet injector – a device that uses high pressure instead of a needle to propel insulin through the skin into the body.

Lipoatrophy – loss of fat under the skin, resulting in small dents. It may be caused by repeated injections of insulin in the same spot.

Lipohypertrophy – buildup of fat below the surface of the skin, causing lumps. It may be caused by repeated injections of insulin in the same spot.

Lispro insulin – a rapid-acting insulin analogue in which the position of two amino acids are switched. The resulting insulin analog is faster acting than regular insulin (short-acting insulin). On average lispro insulin starts to lower blood glucose within 5 minutes after injection. It has its strongest effect 30 minutes to 1 hour after injection but keeps working for 3 hours after injection. It can be injected immediately before a meal, compared with regular, which should be injected 30 minutes or more before a meal.

Long-acting insulin – a type of insulin that starts to lower blood glucose within 4 to 6 hours after injection and has its strongest effect 10 to 18 hours after injection.

Macrosomia – a condition in which a baby is considerably larger than normal (birth weight greater than 4000 grams).

Nephropathy – diabetic kidney disease, a slow deterioration of the kidneys and kidney function that in more severe cases can eventually result in kidney failure. It is also known as end-stage renal disease, or ESRD.

Neuropathy – progressive damage to the nervous system caused by diabetes, which leads to a loss of feeling in the hands and feet.

Nocturnal hypoglycemia – hypoglycemia occurring while the patient is asleep (between the evening injection and getting up in the morning).

Noninvasive blood glucose monitoring – a way to measure blood glucose levels without having to prick the finger to obtain a blood sample.

NPH insulin – neutral protamine Hagedorn, also called N insulin. On average NPH insulin starts to lower blood glucose within 1 to 2 hours after injection. It has its strongest effect 6 to 10 hours after injection but keeps working about 10 hours after injection.

Pancreas – an organ that makes insulin and enzymes for digestion; it is located behind the lower part of the stomach and is about the size of a hand.

Pancreas transplant – a surgical procedure that involves taking a healthy whole or partial pancreas from a donor and placing it into a person with diabetes.

Prevalence – the number of people in a given group or population who are reported to have a disease.

Rapid-acting insulin – a type of insulin that starts to lower blood glucose within 5 to 10 minutes after injection and has its strongest effect 30 minutes to 3 hours after injection, depending on the type used.

Regular insulin – short-acting insulin; on average, regular insulin starts to lower blood glucose within 30 minutes after injection; it has its strongest effect 2 to 5 hours after injection but keeps working 5 to 8 hours after injection.

Self-monitoring of blood glucose (SMBG) – blood testing done by a person with diabetes with a blood glucose meter or monitor to determine how much glucose is in the blood. SMBG helps people with diabetes and their healthcare professionals make decisions about their medications, diet, and exercise in order to achieve good blood glucose control.

Severe hypoglycemia – hypoglycemia episode requiring assistance from another person or resulting in seizure or coma.

Subcutaneous injection – putting a fluid into the tissue under the skin with a needle and syringe.

Type 1 diabetes – an autoimmune disease that occurs when the pancreas no longer produces any insulin or produces very little insulin, previously called insulin-dependent diabetes or juvenile diabetes. Type 1 diabetes usually develops suddenly and most commonly in younger people under age 30 (in childhood or adolescence) and affects approximately 10% of people with diabetes. There is no cure for this disease, and it is treated with lifelong daily insulin therapy, a planned diet and regular exercise, and daily self-monitoring of blood glucose.

Unit of insulin – the basic measure of insulin. U-100 insulin means 100 units of insulin per millilitre or cubic centimetre of solution. Most insulin made today in the United States is U-100.

INTRODUCTION

Purpose of Assessment

- To review the effectiveness and safety of insulin pump therapy (IPT)
- To review the social considerations for the provision of IPT
- To review the fiscal and economic considerations for the provision of IPT

Research Questions

The Alberta Health and Wellness' Executive Committee accepted the Alberta Health Technology Decision Program's Advisory Committee's recommendation to undertake a STE analysis of insulin delivery systems. The purpose of this report is to address the following questions of interest:

- What is the potential role of IPT in the treatment of Albertans with type 1 diabetes mellitus (T1DM) in Alberta compared to multiple daily injections (MDI)?
- What subpopulation would benefit from IPT compared with MDI (syringe and pen)?
- What are the established criteria for initiating IPT?
- What is the cost-effectiveness of IPT compared with MDI?

BACKGROUND

Technology Definition

Continuous subcutaneous insulin infusion, more commonly known as insulin pump therapy (IPT), is an alternative to insulin injections by syringes or insulin pens. Development of the current models of insulin pumps began in the late 1970s and was refined in the 1990s, when technological advances enabled dramatic reductions in the pump's size, increased safety, and greater ease of use for patients.

An insulin pump consists of a battery-operated, programmable infusion pump with an internal insulin reservoir. The pump is linked by plastic tubing to a cannula that is inserted under the skin, usually in the abdomen, and is kept in place with adhesive dressing. The site of cannula must be changed every 2 to 3 days to avoid skin irritation or infections, and the tubing must be changed every 6 days. The pump is approximately the size of a pager and can be worn discreetly.

The insulin pump is programmed to deliver rapid-acting insulin to the patient continuously to ensure basal blood insulin levels. The rate can be varied throughout the day and night based on the insulin needs of the patient. Immediately prior to eating, the patient manually programs the pump to deliver a larger, supplemental dose (bolus dose) of rapid-acting insulin. The size of the bolus dose is determined by the patient's pre-meal blood glucose levels and the calculated amount of carbohydrates to be consumed. Insulin pump therapy requires that patients measure their blood glucose levels between four and six times per day at a minimum.

Condition Definition

Diabetes mellitus is a chronic disease characterized by high levels of blood glucose. Type 1 diabetes mellitus (T1DM) is associated with the inability to produce insulin and type 2 diabetes mellitus (T2DM) is associated with insulin resistance followed by declining production. T1DM requires

insulin injections from diagnosis, whereas T2DM may require insulin injections only as the disease progresses.

T1DM, characterized by high blood glucose levels that require lifelong insulin therapy, can cause short- and long-term complications in different organs such as the heart, eyes, kidneys, and blood vessels. T1DM can occur at any age but usually is diagnosed in childhood, adolescence, or early adulthood. Causation is unknown, but it is thought to be related to autoimmune, genetic, and environmental factors. It may cause neuro-cognitive dysfunction and behavioural changes in children. In pregnant women, high glucose levels are associated with increased risk of fetal congenital malformation, peri-natal mortality, obstetric complications, and neonatal morbidity.

Guidelines for intensive insulin therapy of T1DM recommend an individualized intensive insulin regimen using either MDI or IPT.

SECTION ONE: SOCIAL SYSTEMS AND DEMOGRAPHICS (S)

Paula Corabian, BSc, MPH, Charles Yan, PhD

The social and systems demographics approach to analysis summarizes available key information on the use of IPT for type 1 diabetes mellitus (T1DM) in Alberta, in Canada, and other countries with developed market economies. This analysis was intended to describe the profile of T1DM (definition, progression, epidemiology, and population dynamics of affected individuals in Alberta, in Canada, and worldwide) and patterns of care for this condition (focusing on insulin therapy recommended by evidence-based guidelines) as well as to identify potential inequities in health status or care across population groups. Social factors associated with the potential introduction of IPT as the primary insulin delivery method for individuals with T1DM in Alberta were also considered.

The social and system demographics approach to this analysis report is intended to address the following questions:

- What is the prevalence and incidence of T1DM in Alberta, in Canada, and worldwide?
- What is the standard of care for T1DM in Alberta, in Canada, and worldwide?
- What is the standard modality for insulin delivery used for T1DM in Alberta?
- How many patients with T1DM would most benefit from IPT in Alberta?
- What is the demand for IPT in Alberta?
- What are the utilization and the discontinuation rates for IPT in Alberta?
- Are there any issues related to acceptability, adherence, or noncompliance when using IPT in Alberta compared to multiple daily injection (MDI)?
- Are there any quality-of-life issues when using IPT in Alberta compared to MDI?
- What are the number and the distribution of diabetes programs, clinics, and facilities that provide IPT services in Alberta?
- What are the number and the distribution of health care practitioners and support staff capable in providing IPT services in Alberta?
- What is the patient/trained practitioner ratio in Alberta?
- Are there any issues related to training and accreditation, access to appropriate treatment options, or quality control when using IPT compared to MDI? Are there ethical or legal issues?
- What are the implications (on society, families and caregivers, and the affected individuals) for the potential introduction of IPT for individuals with T1DM in Alberta?

Methodology

Search strategy

To answer the questions posed for the social and system demographics approach to analysis, the medical literature was searched to identify relevant articles and documents published between January 2004 and July 2009 using key health information resources, including EMBASE, the

Cochrane Library, PubMed/MEDLINE, and Centre for Reviews and Dissemination (CRD) databases (see Appendix S.A for more details). Additional Internet searches were conducted to retrieve grey literature. Reference lists of relevant articles were also browsed to identify more studies. The results were limited to studies involving humans and reported in the English language. The date restriction was applied to ensure that the evidence collected was current and clinically relevant.

The literature search was focused on articles and documents providing information on the etiology of T1DM and those reporting on the incidence and prevalence of T1DM, psychosocial impact of T1DM, patterns of care and type of services provided for people (all ages, males and females) with T1DM (of any duration or stage), and usage of MDI, IPT, or both as insulin delivery methods in Alberta, in Canada, and worldwide.

The search strategy was focused on articles reporting findings from surveys, qualitative research studies, guidelines and consensus statements or position papers, policy papers, overviews, clinical reviews, and discussion papers that were conducted or developed in Canada and other countries with developed market economies.

Also conducted was a search for published local data and information from sources such as the Canadian Institute for Health Information (CIHI), Health Canada, Statistics Canada, Canadian Diabetes Association (CDA), the Alliance for Canadian Health Outcomes Research in Diabetes (ACHORD), the Surveillance Branch of Alberta Health and Wellness, and the College of Physicians and Surgeons of Alberta.

Healthcare providers from diabetes care facilities and clinics in Alberta and three manufacturers supplying insulin pump devices in Alberta and Canada were contacted and asked if they were aware of the number of individuals with T1DM and the number of those treated by IPT or MDI in Alberta or Canada, and for any sources for such information (such as provincial or national insulin pump registers, manufacturers' records, or reports on insulin pump practice in Alberta or Canada). Manufacturers were also asked questions regarding the IPT usage rate and dropout rate; issues related to access, demand for, and barriers to using pump services; training of healthcare providers and patients; the current number and distribution of insulin pump (initiation) centres; and data on trained diabetes healthcare providers and support staff who are capable of providing pump services in Alberta and Canada.

Study selection

The initial and final study selection was conducted by one reviewer using selection criteria developed a priori. The initial study selection was based on titles or abstracts only. Excluded were articles that, on the basis of their abstract, clearly did not meet the inclusion criteria. The final selection was based on full-text articles. Copies of the full text of potentially relevant papers were retrieved and assessed for eligibility based on the selection criteria.

Published articles were included if they reported results on etiology, epidemiology, pathology, screening, diagnosis, treatment, rehabilitation, prevention, (prognosis of) progression, management, or quality of life in T1DM.

Guidelines were included if they provided definitive recommendations for the prevention of T1DM and for screening, diagnosis, and management of people (all ages, both genders) with T1DM (of any duration or stage). Those that referred to diabetes mellitus were included only if they provided recommendations that were specific for T1DM. Considered were only those publicly available evidence-based guidelines that, by virtue of design and quality of reporting, were most likely to provide valid recommendations. Clinical practice guidelines that were not evidence based, such as

consensus statements containing recommendations based only on expert opinion, were included only if they were developed in Canada or provided relevant information regarding the current practice in Canada or Alberta.

Profile of Illness

Diabetes mellitus is a chronic metabolic disorder characterized by the presence of hyperglycemia (higher than normal blood glucose levels) due to defective insulin secretion, defective insulin action, or both (www.eatlas.idf.org, www.diabetes.ca, www.diabetes.org).[1-8] Insulin is a hormone produced by the islet beta cells of the pancreas in response to rising blood glucose levels and mainly regulates the metabolism of carbohydrates, but also of proteins and fats. Absolute or relative insulin deficiency leads to abnormal glucose metabolism and loss of control of blood glucose levels, which increases the risk of developing potentially devastating micro- and macrovascular complications.

On the basis of etiology and clinical presentation of the disorder, diabetes mellitus is classified into four types: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and other specific types (www.eatlas.idf.org, www.diabetes.ca, www.diabetes.org).[1,7,9-12]

This report addresses only T1DM.

Definition, classification, and description of T1DM

T1DM, also known as insulin-dependent diabetes mellitus, childhood-onset diabetes, or juvenile diabetes, encompasses cases that are primarily a result of pancreatic beta cell destruction, loss, or failure (which usually leads to absolute insulin deficiency) and are prone to diabetes ketoacidosis (DKA) (www.eatlas.idf.org, www.diabetes.ca, www.jdrf.ca, www.diabetes.org).[1,3,4,7-9,11-14] It is either immune mediated (in 85% to 90% of cases, beta cell destruction is attributable to an autoimmune process) or idiopathic (in 10 to 15% of cases, neither an etiology nor a pathogenesis is known).

With respect to development, T1DM passes through the preclinical stage (characterized by progressive beta cell destruction or failure without symptoms), the clinical presentation with symptoms, the "honeymoon stage" (a period of relative remission), and the chronic phase of severe or absolute insulin deficiency and lifelong dependence on insulin therapy for survival.[9,10,12,13,15,16] Progressive beta cell destruction or failure occurs at a variable rate and may last for months to years, during which the individual is asymptomatic. T1DM becomes clinically symptomatic when approximately 90% of the pancreatic beta cells are destroyed or fail to produce insulin.

After a diagnosis of T1DM and the start of insulin therapy, a transient (short-lasting) "honeymoon stage" (characterized by an improvement in symptoms and even reduction in insulin dosage) may develop due to production of insulin by the remaining surviving pancreatic beta cells (www.diabetes.ca, www.diabetes.org).[9,10,15,16] Although the progression from the relative remission stage into the chronic phase is usually gradual, it can be accelerated by inter-current illness.

Symptoms

The onset of T1DM is often sudden and the condition is rarely diagnosed before symptoms develop (www.eatlas.idf.org, www.diabetes.ca, www.jdrf.ca, www.diabetes.org).[3,4,7-9,11-13,17-19] Warning signs and symptoms usually develop rapidly and may include increased thirst (polydipsia); increased frequency of urination (polyuria), particularly urination at night (nocturia); tiredness or fatigue; increased hunger (polyphagia); sudden weight loss; recurrent infections; blurred vision or other changes in eyesight; and symptoms of DKA (drowsiness, lethargy, decreased alertness, rapid breathing, dehydration, abdominal pain, nausea, and vomiting). Children may show symptoms of restlessness

or apathy and have trouble functioning at school. In severe cases, decreased consciousness or diabetic coma may be the first sign of T1DM.

Causes

It has yet to be determined what specifically prompts the autoimmune response that destroys the body's ability to produce insulin in T1DM (www.diabetes.ca, www.jdrf.ca, www.diabetes.org, www.eatlas.idf.org).[1,3,7-9,11,14,15,20-24] Available evidence suggests that immune-mediated T1DM is likely prompted by interplay between genetic susceptibility and environmental factors.

Potential risk factors

Potential risk factors for T1DM include early fetal events (such as blood group incompatibility, maternal viral infections, and pre-eclampsia during pregnancy), being ill in early infancy, early exposure to cow's milk components and other nutritional factors (such as cereals or gluten), (early) exposure to viruses and toxins, high birth weight and height, rapid growth during early childhood, and having a parent with T1DM (www.eatlas.idf.org, www.diabetes.ca, www.diabetes.org, www.jdrf.ca, www.cdc.gov).[13,14,19,21,22,24-29] There is, however, no current strong evidence demonstrating a direct link between these factors and T1DM in humans.

Reduced exposure to ultraviolet light and lower vitamin D levels, both of which are more likely found in the higher latitudes, are associated with an increased risk of T1DM.[26,30-32] A long duration of breast feeding, early vitamin D intake, and preschool daycare (as a proxy measure of infections) have been identified as protective factors.[26,27,33]

Several studies have documented a seasonal pattern of T1DM onset, with increased incidence in the winter.[14,31,32] In both the Northern and Southern Hemispheres, the incidence declines during summer months. The pattern of seasonality of T1DM onset has been observed in both males and females and in all age groups and it appears to be more prominent in countries with large differences between summer and winter temperatures. The role the climate plays in the development of T1DM is unclear.

Complications

If left untreated or improperly managed, T1DM can result in a variety of acute and chronic complications that are related to the disease itself, to its treatment, or to both (www.cdc.gov, www.eatlas.idf.org, www.jdrf.ca, www.diabetes.ca, www.diabetes.org).[1,9-13,34-38] The likelihood of developing complications appears to depend on the interaction of many factors, including metabolic control, genetic susceptibility, lifestyle, pubertal status, and gender.

T1DM can be complicated by the presence of some other diseases.[9,10,12,13,15,34]

Acute complications

T1DM and its management have two major and frequent acute complications: DKA and hypoglycemia (www.diabetes.ca, www.diabetes.org, www.jdrf.ca).[1,9-13,36,37,39,40] These acute complications reflect the difficulties of maintaining a balance between the recommended insulin therapy, dietary intake, and exercise.

DKA is a metabolic state resulting from acute hyperglycemia that can be life threatening (www.jdrf.ca, www.diabetes.ca, www.diabetes.org).[1,9-13,36,37,39,40] It occurs in individuals with newly diagnosed T1DM and in those with established T1DM. Risk factors include presence of infection, omission or under-use of insulin (noncompliance with insulin therapy), and equipment malfunction (for insulin pumps).

Hypoglycemia is the most frequent acute complication of T1DM and is the major factor limiting intensive management regimens aiming for near-normal glycemia (www.diabetes.ca, www.diabetes.org, www.jdrf.ca).[1,9,13,39] It can be caused by excessive insulin administration, insufficient food intake, increased alcohol intake, excess exercise, or a combination of these, and it is the most common complication of intensive insulin therapy. The blood glucose level at which hypoglycemic symptoms occur varies considerably between individuals and within the same individual. Increasing frequency of hypoglycemia can lead to hypoglycemia unawareness, a condition in which individuals become insensitive to hypoglycemic symptoms.

Risk factors for severe hypoglycemia (defined as a hypoglycemic episode that the individual needs others to assist in treating) include age group (for example, very young children who cannot detect hypoglycemia), attempting tight blood glucose control, long-term diabetes, noncompliance with treatment, and infections (www.jdrf.ca, www.diabetes.ca, www.diabetes.org).[1,2,9-13,36,39] It occurs frequently at night, during sleep, or in the absence of hypoglycemia awareness. Asymptomatic nocturnal hypoglycemia is common.

Chronic complications

Chronic complications associated with T1DM arise from the damaging effects of prolonged (chronic) hyperglycemia and have been linked to poor glycemic control and the duration of the disease (www.diabetes.ca, www.diabetes.org, www.jdrf.ca).[1,9,10,13,37,39,41] These include microvascular complications (such as diabetic retinopathy, nephropathy, and neuropathy) and macrovascular complications (including circulatory and cardiovascular events such as stroke and myocardial infarction).

A multinational, cross-sectional study of complications in T1DM that was sponsored by the World Health Organization (WHO) reported a great variation in the geographic distribution of retinopathy, nephropathy, and neuropathy.[35] Drawing on their findings, investigators have suggested that the performance of the local healthcare system and the local social distribution of wealth and purchasing power may play important roles in explaining the geographic variation of diabetes complications.

A large study on microvascular complication in T1DM in the United States reported a doubling of the risk for developing diabetic retinopathy and neuropathy in affected females compared to affected males.[42]

Psychological morbidity

Psychological and psychiatric morbidity (including emotional and behaviour disorders and depression) is increased in individuals with T1DM (www.diabetes.ca, www.diabetes.org, www.jdrf.ca).[1,9,10,12,13,17,37,39] T1DM and its management impose a number of psychological stresses on both the affected individual and his or her family and caregivers. Fluctuations in blood glucose levels may contribute directly to alterations in behaviour and mood, with increased restlessness and irritability and reduced capacity to concentrate. Anxiety, depression, or both are frequent consequences of T1DM and may be more severe in affected individuals. Difficulty evolves in T1DM management and treatment when psychological and psychiatric disorders contribute to poor self-care and glycemic control.

Diseases complicating T1DM

Several autoimmune diseases are associated with an increased incidence in individuals with T1DM (www.diabetes.ca, www.diabetes.org, www.jdrf.ca).[2,9,10,12,17,34,37,39] The most frequently associated autoimmune diseases with T1DM are thyroid and celiac diseases. Coexisting autoimmune diseases may lead to diabetic decompensation via various patho-physiological mechanisms.[34]

The presence of some other disorders may complicate T1DM; these include respiratory diseases, infectious diseases, allergic diseases, hyperlipidemia, microalbuminuria, gastrointestinal infections, gynecological problems, and urinary infections.[2,9,10,13,15,17,34,38] These diseases represent stressful stimuli and cause sick days.

Complications of T1DM in specific populations

In children and adolescents with T1DM, the most common complications include hypoglycemia, hyperglycemia, DKA, and psychological and psychiatric morbidity (www.cdc.gov/diabetes, www.jdrf.ca, www.diabetes.ca, www.diabetes.org, www.eatlas.idf.org).[1,3,10,11,36,39] Among young patients, boys of any age are at higher risk of developing hypoglycemia, probably due to their relatively higher rate of glucose utilization. Severe hypoglycemia may cause permanent neuro-psychological impairment in younger children (less than 6 years of age). Hypoglycemia is rated as the most anxiety-promoting feature of T1DM by both children and parents.

T1DM in children and adolescents is associated with higher rates of psychological and psychiatric disorders, including adjustment disorders, cognitive disorders, behavioural and conduct disorders, major depression, anxiety disorders, and eating disorders (www.cdc.gov/diabetes, www.diabetes.ca, www.diabetes.org, www.eatlas.idf.org, www.jdrf.ca).[9,12,13,39,41] Psychological and psychiatric disorders in childhood increase the risk of subsequent psychological and psychiatric disorders in adolescence and adulthood.

The pathogenesis of long-term vascular complications of T1DM including retinopathy, nephropathy, neuropathy, and cardiovascular disease begins in childhood, although clinical manifestations of these complications are uncommon before adulthood (www.cdc.gov, www.diabetes.ca, www.diabetes.org, www.eatlas.idf.org).[9,13,39,41] More than 50% of patients with diabetes onset during childhood develop microvascular complications 10 to 12 years later.

T1DM in pregnancy is associated with adverse pregnancy outcomes (www.cdc.gov).[9,10,17,38,42-47] Pregnant women with pre-existing diabetes are at higher risk for miscarriages, pre-eclampsia, preterm labour and delivery, delivery by Caesarean section, and retinopathy. Women with T1DM are at risk of hypoglycemia and hypoglycemia unawareness during pregnancy, particularly in the first trimester. Pre-existing nephropathy and retinopathy may worsen.

Pregnancy in women with T1DM and poorly controlled T1DM before and through conception and during the first trimester of pregnancy increases the risks of congenital malformations in the fetus and may have significant adverse effects on the developing fetus (such as excessive fetal weight gain, breathing problems and delayed lung development, or low blood glucose) and may increase the risk for birth defects and for diabetes in the future (www.cdc.gov).[9,10,38,42-47] Presence of diabetic nephropathy in the first 20 weeks of pregnancy is associated with an increased risk of intrauterine growth retardation and fetal distress. DKA during pregnancy is a major cause of fetal death.

Epidemiology of T1DM and population dynamics of affected patients

In developed countries T1DM contributes to approximately 10% of all diabetes mellitus cases (www.diabetes.ca, www.diabetes.org, www.albertadiabetes.ca, www.eatlas.idf.org, www.jdrf.ca),[1,7,8,11,12,15,20,22,23,26,27] affecting 0.5% to 1% of the total population during a lifetime.[22] It can develop at any age but usually appears between infancy and the late 30s, most typically in childhood or adolescence. Three-quarters of all cases are diagnosed in individuals less than 18 years of age. Males and females tend to be equally vulnerable.

The rates of T1DM vary based on age, gender, geography, and race or ethnicity (www.eatlas.idf.org).[1,12,14,18,19,23,26,27,33,48,48-50] Incidence rates increase with age until puberty. In areas with high prevalence rates, a bimodal variation in incidence that shows a peak in early childhood and a second greater peak of incidence during early puberty has been reported. The influence of gender varies with the overall incidence rates. Males are at greater risk in regions of high incidence and females appear to be at greater risk in low-incidence regions. After the pubertal years the incidence rate drops in young women but remains relatively high in young adult males up to the age 29 to 35 years, suggesting the existence of gender-dependent factors that regulate the autoimmune process.

T1DM has wide geographic variation in incidence and prevalence (www.eatlas.idf.org, www.jdrf.ca).[1,14,18,19,21,26,48,51-53] Incidence is lowest in China and Venezuela (0.1 per 100,000 per year in China and Venezuela) and highest in Finland (40.9 per 100,000 per year).[19] Within the seven major insulin markets (the United States, Japan, France, Germany, Italy, Spain, and the United Kingdom) the prevalence of T1DM ranges from 0.2% (Japan) to 0.7% (Germany).[1] In these countries alone more than 3.1 million (with an expected increase to 3.4 million in 2011) people are affected.[1]

T1DM appears to be more common in Caucasians and individuals of northern European descent and, specifically, Mediterranean groups and it is less common in people of Asian and African descent (www.cdc.gov, www.eatlas.idf.org, www.diabetes.org, www.diabetes.ca).[20] In North America it is more likely to develop in non-Hispanic white people than in American Indians, American Africans, Asians or Pacific Islanders, or Hispanics. There is evidence to suggest that when immigrants from an area with low incidence move to an area with a higher incidence, their rate of T1DM tend to increase toward the higher level.

Trends in T1DM incidence and prevalence worldwide

An increasing trend in incidence and prevalence of T1DM has been demonstrated in most regions of the world over the past few decades, by an average of 3% per year, mainly in young children, with clear indications of great geographic differences (www.eatlas.idf.org, www.cdc.gov).[14,18-20,23,24,27,28,29,51,54,55] Apart from the rise in the incidence, factors contributing to a continued upward trend in the global prevalence include better diagnosis of T1DM, improved availability of insulin and access to treatment, and increases in overall population growth. There are also indications of a decrease in deaths from both unrecognized DKA in children and from late complications in young adults in some developed countries, which could lead to an additional increase in the T1DM prevalence.

Substantial variations are observed between nearby countries with differing lifestyles, and between genetically similar but socio-economically disparate societies. (www.eatlas.idf.org, www.cdc.gov).[14,18-20,23,24,28,29,51,55] There are also within-country variations in incidence in several countries (www.eatlas.idf.org).[18,19,26,27,33,48] These variations, the constant increase in T1DM incidence over a relatively short period of time, and data from migration studies implicate both genetic and environmental factors in the development of T1DM.

The increase in incidence in T1DM has been shown in countries having both high and low prevalence, and the greatest increase is observed in children under 5 years of age (www.eatlas.idf.org).[18,19,26,27] However, there is an indication of a steeper increase in some of the low-prevalence countries and an association between the risk increase and gross national product estimates. These findings suggest that part of the increasing trend may be due to potentially preventable lifestyle factors.

Although T1DM usually accounts for only a minority of the total burden of diabetes in a population, it is the predominant form of the disease in children and adolescents in most developed countries

(www.cdc.gov, www.jdrf.ca, www.diabetes.org, www.diabetes.ca, www.eatlas.idf.org).[1,2,8,11,12,15,18-20,23,26,27] According to the Diabetes Atlas produced by the International Diabetes Federation (IDF, www.eatlas.idf.org), of the worlds' 1.8 billion children (less than 14 years of age) in 2006, approximately 440,000 have T1DM, representing a prevalence of 0.02% with about 70,000 new cases diagnosed annually and an average annual increment in incidence of 3%.

Data emerging from the WHO-sponsored Diabetes Mondiale (DiaMond) study[18,19] and from the IDF Diabetes Atlas (www.eatlats.idf.org) indicate that Asia, Africa, and South and Central America have relatively low rates of childhood T1DM (0 to 14 years of age), whereas Northern Europe, North America, New Zealand, and Australia have the highest rates. The reason for the north-south geographical gradient in T1DM incidence is unknown.[14] However, climate differences and increased prevalence of virus infections in children from the Northern Hemisphere as compared with Southern Hemisphere may be involved in the variation seen between the northern and southern regions of Europe and North and South America.

Information on mortality rates is difficult to ascertain without national or provincial registers on T1DM, and mortality in undiagnosed diabetes is probably a large but hidden problem in the global perspective (www.eatlats.idf.org).

Trends in T1DM incidence in North America

According to earlier estimates, increases in T1DM incidence in the United States and Canada are similar to those observed in other parts of the world for children under 15 years of age (www.eatlas.idf.org).[14,18,19,26,27,33,48,53] According to the data reported by the DiaMond Project Group, the incidence rates based on 1990 to 1999 data varied from high in the United States (11 per 100,000 per year with an annual change of incidence of 5.5%, 95% CI 3.0 to 8.0) to very high in Canada (25 per 100,000 per year; with an annual change of incidence of 5.1%, 95% CI 1.9 to 8.5).[19] Data from Canada were reported for Edmonton (1990 to 1999 data, 75% to 96% estimate of ascertainment, incidence rate for boys of 23.0, for girls 23.6, and total 23.3, 95% CI 20.5 to 26.4), Calgary (1990 to 1999 data, 100% estimate of ascertainment, incidence rate for boys of 20.3, for girls 20.9, and total 20.6, 95% CI 18.5 to 22.7), and Prince Edward Island (1990 to 1993 data, 100% estimate of ascertainment, incidence rate for boys of 28.0, for girls 20.89, and total 24.5, 95% CI 16.4 to 35.2).

Three other Canadian provinces have previously reported childhood T1DM incidence rates.[26,27,33,48] Manitoba reported an incidence of 20.4 per 100,000 in children under 15 years of age from 1985 to 1993. The reported mean incidence for Montreal in the province of Quebec (1971 to 1985) among children 0 to 14 years of age was 10.1 per 100,000. The lowest incidence was reported for Toronto in Ontario (1976 to 1978), with a mean incidence of 9.0 per 100,000 in children under 19 years of age.

T1DM in the United States

In response to the lack of reliable data on changes over time in diabetes mellitus rates in the United States, the Centers for Disease Control and Prevention and the National Institutes of Health funded a 5-year, multicentre study, SEARCH for Diabetes in Youth, to examine diabetes among children and adolescents (0 to 19 years) (www.cdc.gov/diabetes).[53] Based on 2002 and 2003 data, the SEARCH study found the following:

- Annually 15,000 youth (0 to 19 years of age) in the United States were newly diagnosed with T1DM.

- The rate of new cases among youth was 19.0 per 100,000 each year for T1DM, and non-Hispanic white youth had the highest rate of new cases.
- Among youth under 10 years of age, most diabetes cases are T1DM regardless of race or ethnicity. In this age group the highest incidence of T1DM was observed in non-Hispanic whites (19 per 100, 000 per year for 0 to 4 years old, and 28 per 100,000 per year for 5 to 9 years old) and lowest among American Indian (4.1 and 5.5 respectively), and Asian or Pacific Islander children (6.1 and 8.0 respectively).
- Among older youth (age groups: 10 to 14 years and 15 to 19 years) the highest incidence of T1DM was in non-Hispanic white youth (33 per 100,000 per year and 15 per 10,000 per year respectively), followed by African American (19.2 and 11.1 respectively), Hispanic (17.6 and 12.1 respectively), Asian or Pacific Islanders (8.3 and 6.8 respectively), and American Indian (7.1 and 4.8, respectively).
- Rates were very similar in females and males (RR, 1.028; 95%CI 1.025 to 1.030).
- Overall across all racial and ethnic groups and sex, the highest rates of T1DM were observed among 5- to 9-year-old and 10- to 14-year-old youth ($P < 0.001$ for each group versus 0- to 4-year-old youth), although this was largely driven by the age pattern in non-Hispanic white youth.

T1DM in Canada

In Canada, over two million people have diabetes, and that number is expected to reach 2.6 million by 2011 (www.jdrf.ca, www.diabetes.ca).[56] Approximately 10% of Canadians with diabetes have T1DM. According to the Juvenile Diabetes Research Foundation, currently over 240,000 Canadians live with T1DM (www.jdrf.ca).

Canada has one of the highest incidence rates of T1DM in children (0 to 14 years of age) in the world, with an annual change of incidence of approximately 5% (www.jdrf.ca, www.eatlas.idf.org).[19] IDF Diabetes Atlas estimated the incidence rate for Canadian youth (0 to 14 years of age) at 21.7 per 100,000 in 2007 (www.eatlas.idf.org). The estimated incidence rate increased with age (14.7 for 0- to 4-year-olds, 24.0 for 5- to 9-year-olds, and 26.3 for 10- to 14-year-olds). The estimated number of prevalent cases of T1DM among Canadian children (0 to 14 years of age) was 8400 in 2007.

Several studies reported recent estimates of T1DM rates in Newfoundland and Quebec.[8,26,27,48] The reported estimates showed geographical differences in incidence rates between the two provinces and between various regions within each province. Different ascertainment methods and case definitions were used in these studies, however, making comparisons across studies difficult.

In 2008 Newhook et al.[26] published the results from a cohort study conducted to determine the incidence of T1DM among children aged 0 to 14 years inclusive in Newfoundland and Labrador from 1987 to 2005. All children who were diagnosed with T1DM from 1987 to 2005 and who lived in Newfoundland at the time of diagnosis were included in the study except First Nations children. Cases identified during this period were ascertained from hospital medical records, diabetes registries kept by diabetes nurse educators, and a registry for the Provincial Diabetes Camp from years 1987 to 2005.

The investigators found that 732 children aged 0 to 14 years (384 males and 348 females) were diagnosed with T1DM over the period 1987 to 2005.[26] The T1DM incidence over the study period was 35.08 per 100,000 per year (95% CI 32.54 to 37.62) and increased linearly at the rate of 0.78 per

100,000 per year. There was no significant difference between the rates for males and females in the 0- to 14-year age group (35.98 per 100,000 per year and 34.14 per 100,000 per year, respectively; P = 0.239). However, there was a significant difference between the rates for males and females in the 0- to 4-year age group (31.61 per 100,000 per year and 19.05 per 100,000 per year respectively; P = 0.001).

The T1DM incidence among children (0 to 14 years) over 1987 to 2005 was high throughout the province of Newfoundland and Labrador.[26] The highest rates were located in the Northern Peninsula (43.2 per 100,000; 95% CI 30.8 to 58.4), Notre Dame Bay (41.4 per 100,000 per year; 95% CI 30.8 to 51.5), and Humbar District (40.5 per 100,000 per year; 95% CI 30.9 to 51.8). For the Labrador region the incidence was 31.39 per 100,000 per year (95% CI 21.94 to 40.65). The lowest rate was located in the South Coast (18.3 per 100,000 per year; 95% CI 10.5 to 29.2).

Another prospective cohort study was conducted by Newhook et al.[27] to determine the incidence of childhood T1DM from 1987 to 2002 among children aged 0 to 14 years in the Avalon Peninsula of Newfoundland. Participants were ascertained from diabetes registers kept by diabetes nurse educators from 1987 onward, hospital medical records from 1987 to 2002, and a registry for the Provincial Diabetes Camp from 1987 to 2002. The investigators identified 294 new cases of T1DM among children aged 0 to 14 years, with an overall incidence 35.93 per 100,000 per year (95% CI 31.82 to 40.03). There was no significant difference between the incidences for males and females (36.15 and 35.69 per 100,000 per year, respectively; P= 0.752). The estimated rate at which the incidence was increasing per year was 1.25. Over the study period the T1DM incidence rate was 24.95 per 100,000 per year for the 0- to 4-year age group, 37.01 per 100,000 per year for the 5- to 9-year age group, and 43.62 per 100,000 per year for the 10- to 14-year age group. From 1998 to 2002 the incidence for the age group 0 to 14 years remained greater than 40 per 100,000 per year.

Alaghehbandan et al.[33] conducted a population-based study to calculate incidence and hospitalization rates of childhood T1DM in Newfoundland and Labrador and to assess hospitalization trends and associated factors. Data for all patients aged 0 to 19 years with a diagnosis of T1DM were obtained from the clinical database management system for a 7-year period (1995 April 1 to 2002 March 31). Incidence was calculated for the 0- to 7-year age group.

Over the study period, the overall T1DM incidence was 19.0 per 100,000 person-years (P-Y) (95% CI 5.8 to 32.2) among children aged 0 to 7 years and 22.1 per 100,000 P-Y among children aged 0 to 4 years.[33] Incidence rates among males and females were 21.8 and 16.1 per 100,000 P-Y, respectively (P > 0.05). Age groups of 2 to 3 years and 4 to 5 years had the highest incidence rates (22.6 per 100,000 P-Y and 28.8 per 100,000 P-Y, respectively). Incidence rate of T1DM among males aged 0 to 4 years was higher than for females aged 0 to 4 years (24.4 and 19.1 per 100,000 P-Y, respectively; P > 0.05), which is similar to the results obtained by Newhook and colleagues.[26,27]

These findings suggest that childhood T1DM is of particular importance in Newfoundland and Labrador, where the incidence has been found to be the highest in North America and one of the highest incidence rates in the world.[26,27,33] The reported incidence was increasing in all age groups for both males and females over a 19-year study period. Hospitalization rates for DKA and non-DKA slightly increased between 1995/1996 and 2001/2002.[33] Age and sex patterns suggest that DKA is a particular challenge among adolescent girls.

It has been suggested that the high incidence of T1DM in Newfoundland and Labrador might be caused by one or more environmental factors (such as early infant diet, vitamin D insufficiency, and increased height, weight, and body mass index during early childhood), triggering the condition in genetically predisposed individuals (its population is unusual in the investigation of complex disease

because of its settlement history, its subsequent founder effect, and its geographical isolation).[26,27,32] The incidence of T1DM in this province is temporarily related to exposure to ultraviolet B radiation.[31,32]

Legault and Polychronacos[48] gathered data through a government allocation program to determine the annual incidence of T1DM in Quebec in the pediatric population (0 to 18 years of age) between 1989 and 2000 and to analyze trends and age of presentation during the same period. The investigators found no evidence of increase in number of children diagnosed with T1DM in Quebec over the 12-year period and reported a steady number of new diagnosed cases (approximately 240 per year). Fifty-three percent were males; this was also steady over time. The age at presentation has not changed, and the incidence in the younger age groups (less than 5 year old) was reported stable over the study period. The latest annual incidence rate (in 2000) was estimated at 15 per 100,000 per year, and the 2000 distribution data showed peaks of incidence in the 13-year-old subgroup (25 per 100,000 per year) and the minimum incidence in less than 1 year-old subgroup (1 per 100,000 per year).

Geographical differences among regions were found in the Quebec study by comparing regions of origin of the cases reported.[48] Some remote regions reported more cases per capita than the more populated regions. Regional incidence varied from 0 (no cases) to 24 per 100, 000 per year. The administrative area of Montreal reported an incidence of 14 per 100,000 per year, an estimate higher than the data of 1983 (9.3 per 100,000 per year). The 1983 data were gathered through a review of a representative sample of Montreal area hospitals' admission records, and the incidence rates were gathered on children up to 14 years old.

According to data published in 2002 by the Institut National de Santé Publique du Québec, approximately 28,000 adults have T1DM and 2000 to 2500 youths from 0 to 17 years of age have T1DM.[8]

It has been estimated that about 750 to 900 individuals develop T1DM each year in Ontario.[29]

T1DM in Alberta

According to data recently published by the Alberta Diabetes Surveillance System (ADSS), the total number of people living with diabetes in Alberta (ages 1 year and older) is 163,857 (more than 1 in every 20 people) (www.albertadiabetes.ca, accessed 14 October 2009). Although the ADSS does not differentiate between T1DM and T2DM, it estimates that 5% to 10% of all people with diabetes have T1DM, which means that 8193 to 16,386 Albertans have T1DM.

Table S.1 provides information on the number of individuals diagnosed with T1DM who accessed the healthcare system in Alberta in fiscal years 2005/2006, 2006/2007, and 2007/2008 (based on data from Alberta Health and Wellness inpatient, ambulatory, and physician claim datasets). In Table S.1 an individual being counted in 2006 was counted in 2007 and 2008 if she or he accessed health care during these years. Table S.2 summarizes the prevalence data for the fiscal year 2007/2008 for each age group based on data from Alberta Health and Wellness. The section in this report entitled "Economic Evaluation" describes in detail how individuals were classified as having T1DM and provides more information on the method used to differentiate patients with T1DM from those with T2DM.

Table S.1: Individuals with T1DM who accessed the healthcare system in 2006 to 2008

Population	2005/2006			2006/2007			2007/2008		
	Females	Males	Total	Females	Males	Total	Females	Males	Total
Children (0 to 6 years)	111	145	256	108	138	246	106	152	258
Adolescents (7 to 18 years)	798	841	1639	777	800	1577	825	876	1701
Adults (19+ years)	8722	10,561	19,283	9711	11,726	21,437	9781	12,246	22,027
Pregnant women	474	—	474	740	—	740	865	—	865
Total			21,652			24,000			24,851

Table S.2: Type 1 diabetes mellitus prevalence, 2007/2008

Group	Females	Males	Overall
Children (0 to 6 years)	0.070%	0.096%	0.083%
Adolescents (7 to 18 years)	0.308%	0.310%	0.309%
Adults (19+ years)	0.746%	0.954%	0.849%

Burden of T1DM

The burden of T1DM includes nonmonetary and monetary elements (www.jdrf.ca, www.diabetes.ca, www.diabetes.org, www.eatlas.idf.org).[2,8-10,12,13,39,57] Affected individuals and their families bear the cost of T1DM through shorter length of life, deteriorating health, changes in quality of life (QoL) or disability, great out-of-pocket expenses, and inconvenience. Life expectancy for people with T1DM may be shortened by as much as 15 years (www.diabetes.ca/about-diabetes/what/prevalence). QoL effects may be as deleterious as premature death. The great monetary cost of managing T1DM and its complications, especially for the uninsured or underinsured individuals, may compromise access to adequate or optimal medical care and supplies. Living with T1DM means living a very structured lifestyle in order to achieve and maintain blood glucose levels near normal values while avoiding associated acute complications.

These personal burdens translate into significant costs for the society as a whole (www.diabetes.ca, www.diabetes.org, www.jdrf.ca, www.eatlas.idf.org).[2,8,57] Although estimates of medical and social costs of T1DM appear less frequently in the literature, earlier reports from England, Wales, Israel, and Spain demonstrated meaningful medical expenses in T1DM, both on a short-term and on a lifetime basis, related to the daily management of the disease and to the treatment of chronic complications.[2] The financial burden is also spread across all sectors of the society in the form of higher insurance premiums and taxes, productivity loss and reduced earnings, and reduced standard of living and QoL.

In terms of social costs of T1DM, several studies noted higher rates of disability and work-related absenteeism in persons with T1DM, particularly in those with chronic complications.[2] The impact of T1DM may also be felt in ways that are less easily quantifiable, such as the influence it may have on the insurance and employment experiences of affected individuals. In addition, health, life, and

sometimes automobile insurance may be more difficult to obtain for a person with T1DM. Individuals may face limitations in the type of jobs available for them (for example, employment in commercial driving is limited because of concern for hypoglycemia).[2]

In summary, T1DM places a heavy burden on the affected individual, their family, the healthcare system, and society.

Patterns of Care

Prediction, prevention, and screening of T1DM

The etiological process of T1DM can be identified and subcategorized, and for the vast majority of cases its onset can be predicted if appropriate determinations are performed.[9-16] T1DM is usually immune mediated and characterized by the presence of multiple diabetes related auto-antibodies, which identify the autoimmune processes that lead to beta cell destruction. An individual's risk of developing this condition has been estimated by considering family history of T1DM with attention to age at onset and sex of the affected relatives and by profiling serologic, immunity, and genetic markers using a combination of auto-antibody measurements, intravenous glucose tolerance testing, and genetic typing. Currently such measurements are available only in centres involved in clinical research.

Although relatively good predictions of T1DM can be obtained by detecting auto-antibodies in one's serum, methods to prevent it are still in the investigational stage (www.diabetes.org, www.diabetes.ca).[2,9-12,15,16,58] Given that the various measurements for predicting T1DM are not universally available, and in the absence of convincing evidence for interventions to prevent or delay the development of T1DM, neither screening of any population nor intervention in the preclinical phase are recommended outside the context of defined or formal clinical research studies.

Diagnosis of T1DM

Diagnostic criteria for diabetes mellitus are based on blood glucose measurements and the presence or absence of symptoms (www.diabetes.org, www.diabetes.ca).[3,7,9,10,12,1741,59] According to recommended criteria, a diagnosis of T1DM can be made if:

- the fasting venous plasma (blood) glucose concentration is greater than or equal to 7.0 mmol/L (126 mg/dL) or
- characteristic symptoms and signs are present and the casual (random) venous plasma glucose concentration is greater or equal to 11.1 mmol/L (200 mg/dL) or
- the plasma glucose concentration taken at least 2 hours after eating is greater or equal to 11.1 mmol/L (200 mg/dL) in a 75 g oral glucose tolerance test (OGTT).

The use of the glycosylated hemoglobin (A1C) test for the diagnosis of diabetes is not recommended in the currently published guidance.[9,10,17,41,59] The A1C test measures the average blood glucose level during the previous 2 to 3 months and is used to monitor glycemic control in people with known diabetes mellitus.

An International Expert Committee with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation was convened in 2008 to consider the current and future means of diagnosing diabetes in nonpregnant individuals.[60] The consensus view of the International Expert Committee is that "the A1C assay may be a better means of diagnosing diabetes than measures of glucose levels. The diagnosis of diabetes is made if the A1C level is > 6.5%. Diagnosis should be confirmed with a

repeat A1C test unless clinical symptoms and glucose levels >200 mg/dl (>11.1 mmol/l) are present." The report of the International Expert Committee may serve as a stimulus to the international community and professional organizations to consider the use of the assay for the diagnosis of diabetes.

Differentiating T1DM from T2DM is based on patient characteristics, history, and lab tests, if appropriate.[9,10,12,13,17,59] In borderline diagnostic situations the presence of autoimmune markers is of assistance in differentiating between T1DM and T2DM.

Generally individuals with T1DM present with acute symptoms and marked elevated blood glucose levels, and most cases are diagnosed soon after the onset of hyperglycemia.[3,9,10,12,13,59] In the absence of symptoms, it is recommended that both aforementioned plasma glucose criteria be met and repeated on another day for a diagnosis of diabetes to be made.

Diagnosis of T1DM in children and adolescents is similar to that in adults (www.diabetes.ca, www.diabetes.org).[3,10,12,13,17] T1DM in childhood usually presents with severe symptoms, very high blood glucose levels, marked glycosuria, ketonuria, and frequently DKA (in approximately 30% of children with newly diagnosed T1DM). An oral glucose tolerance test is not recommended for routine use in making the diagnosis of T1DM in childhood.

Management of T1DM

Successful management of T1DM is currently based on appropriate and effective diabetes and nutritional education (adapted to each individual's age, maturity, stage of diabetes, lifestyle, and culture), insulin replacement therapy, blood glucose monitoring, nutritional planning, physical activity and exercise, and psychological adjustment and wellbeing of the whole family (www.diabetes.ca, www.diabetes.org).[1,3,7-13,17,36,47,61,62] The subcutaneous administration of insulin is the basis of therapy for T1DM, and given the availability of numerous and various insulin formulations and mixtures, a wide range of possible regimens exist, from a frequency of up to two injections per day (conventional insulin therapy) to intensive insulin therapy involving three or more injections per day.

Results from various clinical studies published during the past two decades prompted the development of a consensus statement on intensive glycemic control by intensive diabetes management as a therapeutic standard of care for T1DM (www.diabetes.ca, www.diabetes.org).[1-3,7,9-13,17,47,63] This position was confirmed by the Diabetes Control and Complications Trial (DCCT) and its long-term follow-up study, which showed that glycemic control that approaches near-normal glycemia prevents, postpones, or slows the progression of the retinal, renal, and neurological complications.

DCCT, a multicentre randomized controlled trial, conducted between 1983 and 1993, examined the efficacy of the intensive insulin therapy on glycemic control and long-term diabetic secondary complications as compared to the conventional insulin therapy.[63] One thousand four hundred forty-one patients with T1DM from 29 centres were enrolled in the trial between 1983 and 1989 and were randomly assigned to intensive insulin therapy administered either by an external insulin pump or by three or more daily insulin injections and guided by frequent blood glucose monitoring or to conventional insulin therapy with one or two daily insulin injections.[63] During a mean of 6.5-year (ranged from 3 to 9 years) follow-up, intensive insulin therapy significantly reduced A1C levels (median A1C levels of 7.2% with the intensive insulin therapy versus 9.1% with the conventional therapy), which effectively delays and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with T1DM.[63,64]

Other potential benefits of intensive insulin therapy include reduced risk of macrovascular complications, reduced risk of maternal and fetal morbidity or mortality during pregnancy, reduced risk of congenital malformations in the fetus, better linear growth and sexual development in children and adolescents, and better quality of life.

Intensive insulin therapy

Intensive diabetes management is an attempt to achieve and maintain near-normal glycemia (near-normal blood glucose levels) by using intensive insulin therapy and by adjusting for other important factors to approximate normal physiology.[1-3,7,9-13,17,47] Intensive insulin therapy aims to mimic physiological insulin secretion by providing incremental prandial insulin (short- and rapid-acting formulations) coinciding with each meal or snack and continuous basal insulin (intermediate- and long-acting formulations) overnight and between meals or snacks. It involves flexible, multiple-component insulin regimens tailored to the patient's medical needs and lifestyle and guided by frequent blood glucose monitoring. Patients need to follow action plans that guide them in daily self-management, altering insulin doses and timing, food intake, physical activity, or a combination of these in an attempt to achieve their glycemic goals and targets. Patient education, motivation, and dedication are critical to the successful implementation of this therapy. Also very important are the availability of healthcare professionals experienced in diabetes care; strong family support; appropriately educated, motivated, and dedicated parents; and a healthcare team experienced in pediatric diabetes care for younger children.

There are potential problems associated with the use of intensive insulin therapy in T1DM that may negatively affect the patient's QoL, become a vehicle for family conflict, or both.[3,4,6,7,9-13,17,20,34,36,47,62,65-69] In addition to some conditions that may occur after starting insulin therapy (such as insulin edema and local reactions to insulin injections), the intensive insulin therapy is associated with an increased risk of developing difficulties with hypoglycemia (severe hypoglycemia and hypoglycemia unawareness), weight gain, or both. There are also psychological issues associated with the use of both conventional and intensive insulin therapy that may affect the patient's job or school performance, interpersonal relationships, and emotional wellbeing. Potential psychological adverse effects include depression, anxiety and eating disorders, fear of hypoglycemia, and needle phobia, some of which may not become evident until the patient has experienced a period of this therapy and its physiological complications. These psychological issues may lead to poor adherence and noncompliance with the treatment regimen, which, in turn, may lead to poor glycemic control.

According to recently issued recommendations, although glycemic targets should be individualized, for most patients (adults and adolescents) treatment should aim for an level below or around 7.0% in order to reduce the risk of complications.[3,4,6,9,10,12,13,17,59,66,70] In children glycemic targets vary according to age, and they are generally higher (A1C level greater than 7.5% and less than 8.5%) in order to avoid hypoglycemia. During pregnancy a lower glycemic target range is recommended, and, if it is safely achievable, women with T1DM who are planning to become pregnant are advised to maintain their A1C level below or around 6.0%.[10,47]

The available insulin formulations have various activity profiles and work differently in different people depending on various factors such as insulin dose, injection site, injection depth, patient's age and fat mass, presence of lipohypertrophy or lipoatrophy, ambient and body temperature, and level of physical activity.[1,3,7,9-13,17,34,36,38,47,62] Patient selection is essential to the safety and success of intensive insulin therapy, which must be individualized based on the patient's treatment goals, age, maturity, and ability to assume responsibility for making decisions, duration and stage of T1DM, history of hypoglycemia and DKA, and other medical priorities and concerns as well as abilities to

detect symptoms of acute complications and willingness and readiness for implementing the needed lifestyle changes. The choice of insulin formulations and regimen must also be guided by the availability of support from family or friends, patient and family (cultural) preferences and management skills, experience of the healthcare team, and affordability and sustainability.

A successful regimen is subject to ongoing evaluation and modification to balance the patient's risks and benefits.[3-7,9-13,17,34,36,38,47,61,62,66,71] Caution is recommended when determining whether to pursue intensive insulin therapy and target near-normal blood glucose levels for specific subsets of the population with T1DM. Populations requiring special considerations to increase adherence to and compliance with regimens and needing alterations of glycemic goals to avoid acute complications include children and adolescents, individuals with brittle T1DM, and pregnant women with pre-existing T1DM. Patient characteristics that may negatively influence the risk-to-benefit ratio include presence of difficulties with hypoglycemia (e.g., hypoglycemia unawareness, recurrent severe hypoglycemic episodes, or impaired response to hypoglycemia), psychiatric and psychological morbidity or severe psychosocial stressors, alcohol or drug abuse problems, advanced end-stage diabetes complications or life-limiting comorbid illnesses, age less than 6 years, and inability or unwillingness to commit to the required personal effort and involvement.

Delivery methods for intensive insulin therapy

Currently the most commonly recommended intensive insulin therapy regimens for T1DM (including the basal-bolus regimen) are delivered by multiple daily injections (MDI) of long-acting basal insulin and short- or rapid-acting prandial insulin formulations.[3,4,6,9,10,12,13,17,36,47,59,61,62,66,72,73] The MDI regimen combined with frequent blood glucose monitoring (at least four times daily for basal-bolus regimens), carbohydrate counting, and insulin dose (determined using an insulin-to-carbohydrate ratio) allows flexible food choices in terms of size and timing and is accepted by diabetes experts as a "gold standard" method for intensive T1DM management. However, the number of insulin injections required (three or more injections per day) may be a barrier to good glycemic control and represents a major drawback of MDI.

Subcutaneous injection by syringe has been the most commonly used route of insulin administration for daily use by patients with T1DM during the past 80 years or so.[1,3,5,8,9,12,34,36,43,61,65,74,75] To increase the ease of insulin delivery by MDI and improve adherence to and compliance with prescribed regimens, various devices have been developed and used, including insulin pens, automatic injection devices, jet injectors, and indwelling subcutaneous cannulas. Since 1976 researchers have been working on developing continuous subcutaneous insulin infusion (CSII), or insulin pump therapy (IPT), as an alternative to MDI that would make it possible to mimic normal pancreatic function and to thus permit better insulin dose adjustments to avoid acute and chronic complications while avoiding repeated injections.

IPT was used in the intensive control arm of the DCCT.[4-6,8,34,36,43,61,65,66,76] However, at that time (before 1993) the pumps used to deliver intensive insulin therapy were large and cumbersome and had many technical difficulties. Consequently, this technology fell out of favour for some time. In the late 1990s insulin pump manufacturers remodeled their devices, and their popularity has since been increasing. IPT has evolved greatly in the past 20 years, resulting in a much easier-to-use technology that decreased the device size and increased reliability and efficacy in terms of glycemic control. Short- or rapid-acting insulin is administered when using IPT. Depending on the amount of insulin needed, the pump's reservoir can hold up to 6 days' supply. The infusion set for the insulin pump must be replaced every 2 to 3 days, as indicated in the product labeling.

IPT versus MDI

IPT is currently advocated as the most closely related physiologic method of intensive insulin therapy while allowing more flexibility and more precise insulin dosing than intensive MDI (basal-bolus regimen).[1,5,6,8,12,34,61,62,66,72,77] Advocates of IPT believe that it has two main advantages over MDI that may result in less hyperglycemia and a reduction in hypoglycemia. First, IPT might provide less variability in insulin levels than injected long-acting insulin with MDI. Second, IPT offers the opportunity to vary the rate of insulin infusion during the basal period as well as surrounding the meal. In addition, the total insulin requirement per 24 hours usually decreases 15% to 30% after the patient starts with IPT.[1,5,6,8,12,34,61,62,66,72,77]

Another advantage of IPT over MDI is the greater convenience of insulin administration.[1,5,6,8,12,34,61,62,66,72,76,77] Programmable basal rates are delivered automatically with precision and bolus doses, which can be used to adjust insulin dose around meals and physical activities. Convenience may be important in toddlers and younger children (to deal with challenges of administering very small amounts of insulin, which otherwise would need to be diluted) and in children in whom it may be difficult to administer MDI with sufficient accuracy (for example, during school, or daycare time). IPT can also be more convenient than MDI with regard to injection frequency.

A major disadvantage of IPT over intensive MDI is that it is much more expensive, and the additional cost is an obstacle for many patients, particularly for those who do not have health insurance.[1,34,36,61,62,65,72,76,78-80] Since insulin pens have become popular, they greatly simplified the MDI regimens and increased flexibility and portability convenience for MDI users. Improved basal insulin formulation such as glargine and detemir have also become available, and, with the widespread replacement of NPH insulin (characterized by excessive variability in absorption, resulting in an increase in both hypoglycemia and hyperglycemia), the variability of basal insulin delivery may continue to decrease for some MDI users.

Specific but infrequent complications of IPT include reactions and occasionally infections at the cannula site, tube blockage, and pump malfunction (depleted batteries, electrical or mechanical malfunction, or problems with the insulin reservoir, blockages in the infusion set tubes, and the stability or compatibility of the insulin preparations).[4-6,8,34,44,62,65,66,75,76,79,81-83] Hypoglycemia and DKA is most likely to occur when patients do not recognize that the pump is not properly delivering the correct insulin dose or when insulin infusion is interrupted (due to pump malfunction or because the patient inadvertently pulled out the catheter, disconnected the tubing, or did not change the infusion set or site as prescribed). Furthermore, IPT requires the patient-user to be permanently attached to the pump, which can be a psychological barrier for some people.

IPT is not ideal for all patients because it is a labour-intensive process for candidates, their families, and the diabetes team.[4,6,34,44,61,62,65,66,69,75,76,79,84-87] Its adoption may represent an intensive change with the constant need to be accessible to other caregivers, the need for additional skills and supervision, and the need for parents or family to arrange altered supervisory responsibilities, particularly for very young children. Careful selection of IPT candidates is very important for safe and cost-effective use of this technology, which requires high levels of self-care competence and motivation among patients and carers. Appropriate and effective education and ongoing support tailored to the needs of patients and their carers are also very important to ensure a cost-effective use of IPT. The sophistication of current IPT systems also has implications for the healthcare providers who must interpret the substantial amounts of data collected by the devices and downloaded in the clinic. However, many of these aspects are common to intensive MDI.

Potential stressors, benefits, and expectations associated with the conversion from MDI to IPT may differ for the patient and family depending on the patient's medical, psychosocial, and demographic characteristics, levels of support, and prior insulin regimen.[4,6,8,20,43,62,66-69,79,81-83,85,88,89] Results from systematic reviews of the published literature addressing QoL associated with IPT use in children, adolescents, and adults with T1DM noted the paucity of well-designed studies evaluating this outcome. The outcomes have been mixed, with both improvements and no improvements in QoL measures reported. There is no strong evidence against QoL benefits associated with IPT in this population or otherwise, with poor methodology and inconsistent assessment of QoL clouding the issue. Although it is difficult to prove scientifically, it has been suggested that a compelling argument for QoL benefit is that the majority of patients in IPT studies are reported to continue with this method of intensive insulin delivery, even if metabolic improvements are not achieved.

Current practice

Currently both intensive MDI and IPT are recommended to be considered for the delivery of various intensive insulin therapy regimens to achieve glycemic targets and avoid acute complications in individuals with T1DM of all ages.[3,4,6,9,10,12,13,17,34,36,44,47,59,61,62,66,72,90] IPT is recommended when MDI is considered to be impractical or inappropriate. Because both methods are viewed as strongly dependent on patient discipline, skill, and adherence, it is recommended that they be offered only as part of a package of care that involves continuing education, dietary management, instruction on the use of insulin delivery and blood glucose monitoring systems, emotional and behavioural support, and expertise in diabetes care.

In nonpregnant adults the use of basal-bolus regimen delivered by MDI as part of an intensive diabetes management program is the treatment of choice, and IPT is considered when MDI has failed, provided that those receiving the treatment have the commitment and competence to use the therapy effectively.[9,10,17] NICE guidance recommends IPT as an option for MDI users (including, where appropriate, the use of insulin glargine) who cannot maintain A1C level less than 7.5% without disabling hypoglycemia, provided they have the commitment and competence to use IPT effectively.[17]

Guidance on diabetes in pregnancy recommends that women with insulin-treated diabetes should be offered IPT during pregnancy if adequate glycemic control (target A1C less than or equal to 6.1% preconceptually or in the first trimester) is not obtained by MDI without significant disabling hypoglycemia (defined as "the repeated and unpredicted occurrence of hypoglycemia requiring third-party assistance that results in continuing anxiety about recurrence and is associated with significant adverse effect on quality of life").[10,47]

T1DM management in children and adolescents is particularly subject to a variety of challenges specific to various age groups that influence the selection for and implementation of IPT.[3,4,6,9,10,12,13,61,62,66,71,72,78,90] This population is heterogeneous in its presentation of T1DM as well as in the physical, mental, and emotional characteristics of presenting infants, preschool children, older children, adolescents, and their families. Insulin therapy, regardless of delivery method, is complicated by various aspects of childhood, including variable insulin sensitivity, level of self-care, parent or carer support at home and at school or at nursery school or daycare, irregular meal intake, physical activity, susceptibility to hypoglycemia, and communication difficulties. Teenage and adolescent patients must also deal with hormonal and psychosocial changes associated with puberty.

Current clinical practice is to start pediatric patients with new-onset T1DM on at least two daily injections regimens.[9,10,13,17] When the need for more intensive insulin management occurs, consideration should be given to increasing frequency of injections (MDI regimens); change in the

type of basal (long-acting analogue) insulin and/or prandial (rapid-acting analogue) insulin; and change to IPT. A basal-bolus insulin regimen using either MDI or IPT is recommended to be offered as part of an integrated package of care for T1DM. IPT is usually recommended to be considered as an alternative to intensive MDI (including basal analogues) if the level is persistently above the target range for age, hypoglycemia is a major problem, or QoL needs be improved.

It has been suggested that all pediatric patients with T1DM should be considered as potential candidates for IPT, without age limit.[3,4,6,12,62,66,72,79] Thus, IPT may be initiated at diagnosis or anytime thereafter, although prior experience with the use of insulin syringes and pens is important in case of pump malfunction, and the use of MDI regimen matched by carbohydrate counting is recommended before switching to IPT. Suggested indications for IPT include recurrent severe hypoglycemia, unacceptable fluctuations in blood glucose levels regardless of A1C, suboptimal diabetes control, a tendency to develop ketosis, microvascular complications and/or risk factors for macrovascular complications, and for those with good metabolic control but an insulin regimen that unacceptably compromises lifestyle. IPT is also recommended for very young children (especially infants, in whom insulin therapy is hard to manage), children with feeding difficulties, children with needle phobia, adolescents with eating disorders, and competitive young athletes.

According to the American Academy of Pediatrics, baseline eligibility criteria for IPT in very young diabetic children (under 6 years of age) should include having motivated parents with excellent to good understanding of and compliance with diabetes care and demonstrated mastery of carbohydrate counting.[4] Every effort must be made to ensure that parents have realistic expectations of what IPT can and cannot do as well as what will be required to safely manage their child's diabetes with this delivery method.

Alternative therapies

Other types of therapy for T1DM have been developed recently, including pancreas transplant, artificial pancreas, and islet cell transplantation.[1,2,8,9,11,15,36,61,65] Currently they are not part of the therapeutic arsenal that is usually used for T1DM management but are used in a very select group of seriously ill individuals with T1DM.

Current options and standard method of intensive insulin delivery in Alberta

The literature search conducted for this analysis did not reveal any published information on the current options and standard method of delivering intensive insulin therapy for individuals with T1DM in Alberta. Neither did the search results identify any published reports on IPT or MDI practice in Alberta. Healthcare providers from diabetes care facilities in Alberta were contacted and asked for such information and for information on the pump centres in Alberta and the selection criteria they use for IPT. Their responses are summarized in the following commentary.

Alberta diabetes experts have some difficulty in estimating the population requirements for IPT. It is felt that fewer than 5% of patients with T1DM in Alberta would meet criteria of medical necessity and as few as 1% would need IPT to reduce the risk of hypoglycemia.

Data from the Diabetes, Hypertension & Cholesterol Centre (DHCC) in Calgary indicate that 81% of the adults with T1DM seen at DHCC are MDI users, 13% are IPT users, and only 6% use less than three injections per day. Of all pregnant women with T1DM seen in DHCC, 95% to 100% are MDI users. Because MDI and IPT users might be overrepresented in a specialist clinic population, these numbers may not be reflective of community-wide numbers.

Data from Alberta Children's Hospital in Calgary indicate that of all 855 children and adolescents with T1DM that were seen at the diabetes centre by the end of 2008, 641 (75%) were MDI users and 100 (12%) were IPT users. Of all 641 MDI users, 66 (10.3%) were children between 0 and 6 years of age and 575 (89.7%) were children and adolescents between 7 and 18 years of age. Of all 100 IPT users, six (6%) were children between 0 and 6 years of age and 94 (94%) were children and adolescents between 7 and 18 years of age.

Diabetes care facilities that offer IPT services to Albertans with T1DM are located in Medicine Hat, Lethbridge, Calgary, Red Deer, Edmonton, Fort McMurray, and Grand Prairie, with the largest volume of expertise available in Calgary, Red Deer, and Edmonton. IPT services for children and adolescents are offered at diabetes centres in Calgary (Alberta Children's Hospital), Red Deer, and Edmonton (Stollery Children's Hospital). IPT services for adults with T1DM are offered at diabetes centres in Medicine Hat, Lethbridge, Calgary (DHCC on Richmond Road), and Edmonton (University of Alberta and Grey Nuns hospitals). There are also community pharmacy clinics across Alberta (financed by insulin pump manufacturers) that offer IPT initiation.

In Edmonton there are two programs that supervise IPT use by women with T1DM during pregnancy at the Royal Alexandra and Grey Nuns hospitals. In Calgary there are also two programs that supervise IPT use by women with T1DM during pregnancy at the Foothills Medical Centre and Rockyview General Hospital. Among the pregnant women with T1DM in Edmonton, the total of IPT users per year has been approximated at 10 to 15 (maximum 20). It has been estimated that there are more than 20 IPT users per year among the pregnant women with T1DM in Calgary.

A sequential approach is used to selecting individuals with T1DM for IPT in Alberta, based on clinical grounds, with best efforts first being applied to individualized MDI regimens and with appropriate education, diet, and physical activity before offering IPT to those who fail to achieve optimal glycemic control (personal glycemic goals) and avoid acute complications on recommended MDI. For example, pregnant women with pre-existent T1DM who do not and did not gain good glycemic control (defined as A1C less than 6 %) or experience frequent hypoglycemic episodes on MDI would be offered IPT, and women who were on IPT prior to pregnancy would remain on the pump during pregnancy.

In most centres the switch to IPT occurs after potential candidates and their parents, guardians, and caregivers are educated about the IPT advantages and disadvantages to ensure realistic expectations and after the following selection criteria are met:

- The potential candidate has been diagnosed with T1DM for at least 1 year (for children and adolescents) and is mentally and psychologically stable.
- The potential candidate is under the care of an endocrinologist or an internist with experience in diabetes care and has easy access to (can be followed by) a healthcare team (provider) trained and experienced in IPT initiation and monitoring.
- The potential candidate and his or her parents, guardians, and caregivers (for children) desire optimal glycemic control with less variability and are interested in using IPT and motivated to use it appropriately and effectively to achieve this goal.
- The potential candidate and his or her parents, guardians, and caregivers (for children) are willing and able to follow a nutritional plan, count carbohydrates accurately for each meal or snack, and make appropriate adjustments based on blood glucose measurements and carbohydrate intake.

- The potential candidate and his or her parents, guardians, and caregivers (for children) are willing and able to measure blood glucose levels for at least four times a day, record and analyze the results regularly, and make appropriate adjustments.
- The potential teen candidate is willing to allow his or her parents, guardians, and caregivers to help in T1DM management.
- The potential teen candidate is open to wearing the IPT devices everywhere at all times.
- For a potential young child candidate, his or her parents, guardians, and caregivers have a plan in place for blood glucose monitoring and IPT operation when the child is out of their care (i.e., in school or daycare).
- The potential candidate and his or her parents, guardians, and caregivers are willing and able to spend at least 3 days in IPT education sessions and maintain frequent contact (by fax and/or phone) with the diabetes care team for at least 1 month following IPT initiation.
- The potential candidate and his or her parents, guardians, and caregivers have technical ability to operate the IPT device and troubleshoot it when necessary.
- The potential candidate has the financial resources or private healthcare insurance to cover the cost of IPT (the initial cost for the IPT device and the cost for the monthly IPT supplies).
- The potential candidate and his or her parents, guardians, and caregivers are able to obtain, store, and maintain supplies for IPT.

Access to IPT in Alberta

The literature search conducted for this analysis did not reveal any published information on access to IPT in Alberta. Four manufacturers of IPT systems were contacted and asked questions regarding access to IPT in Alberta and in Canada and only three of them (Medtronic of Canada Ltd.; Disetronic Medical Systems Inc., Roche Diagnostics; and LifeScan Canada Ltd., Animas Canada) replied to the request for information. The following commentary summarizes their responses.

The access to IPT typically follows certain STEs:

- A physician or other healthcare professional recommends IPT to the patient or caregiver, or the patient or caregiver expresses an interest in using IPT. Following informed discussions, they select the pump that would meet the potential user's needs and expectations, and the chosen manufacturer is contacted about the patient's interest in IPT.
- A team of manufacturer representatives (sales, and/or clinical) presents and demonstrates the selected IPT system and supplies face-to-face to potential users and answers patient questions. When the patient or caregiver is ready to proceed and is in agreement with the physician or healthcare provider, the manufacturer representatives present available technology options and packages.
- The manufacturer contacts the health insurance provider to verify coverage on behalf of the patient or caregiver. Upon approval, the manufacturer contacts the patient or caregiver to answer any patient questions and verify some details (size of the pump, preferred colour, shipping details, payment arrangements, etc.).

- Trained and certified healthcare professionals initiate and train patients and caregivers face-to-face in one-on-one or small-group sessions on how to use IPT. Online and workbook training are available to supplement face-to-face training. Information kits can be obtained from their certified pump trainers or directly from manufacturers via telephone or websites.
- Live, toll-free technical pump support is available 24 hours a day, 365 days a year.
- Depending on the manufacturer, access to IPT supplies is available either from the manufacturer's order management department or website or from designated pharmacies. Direct-to-home shipment of supplies is available.

Manufacturers identified the availability of health insurance coverage (private or public) for IPT and related supplies as well as the availability of qualified healthcare professionals to prescribe, initiate IPT services, and train and manage IPT users as issues related to access to this technology and/or as barriers to using IPT services in Canada. Patient education on what the IPT can and cannot do and appropriate IPT training and support can influence the patient's acceptance, adherence, and compliance related to the use of this technology.

In Canada several provincial governments offer programs that may help eligible individuals with T1DM in covering the cost of IPT, including insulin pump and related supplies (Medtronic of Canada, personal communication, 31 August and 17 September 2009, http://www.diabetesadvocacy.com/pump_coverage.htm).[91] Ontario has IPT coverage for children, adolescents, and adults. Newfoundland, New Brunswick, Saskatchewan, and British Columbia cover insulin pumps for children and adolescents. Individuals who are eligible for coverage can buy their insulin pumps and related supplies from the vendors approved in these provinces.

Alberta offers assistance to people with low income and without private insurance through the Alberta Monitoring for Health program, which provides CAD 550 per year for those who require insulin (http://www.diabetes.ca/documents/get-involved/AB.govt-approved_.jan09_.pdf, http://www.diabetesadvocacy.com/assistance.htm). The amount of CAD 550 can be used to cover the cost of insulin as well as insulin pump infusion sets. Other ministries with social support programs also provide support for people with low income who suffer from diabetes and require insulin. Injection supplies (needles, syringes, needles for insulin pens, insulin pump tubing, and syringes) are covered through Income Support, Alberta Child Health Benefit, Alberta Adult Health Benefit, and Assured Income for the Severely Handicapped (AISH) programs (http://www.diabetes.ca/documents/get-involved/AB.govt-approved_jan09_pdf, http://www.employment.alberta.ca/AWonline/HB/4706.html). Coverage for insulin pumps is available only if provided through the Health Benefits Review Committee authorization. Many Albertans with diabetes have supplementary or extended health coverage, which includes diabetic equipment (such as insulin pumps) and diabetic supplies, through their employer-sponsored plans (http://www.calgaryhealthregion.ca/supp/hr/benefits/docs/extended_health_plan_una_211_community.pdf, http://www.capitalhealth.ca/nr/rdonlyres/ekm4wk6almt3u5t6exkvnkiq5wwhn5ayz36wwzjttmmdkjt7hcou5xlkuby7c73h7toug7jf4iw56mwcn32hioymbff/health3+hsaa.pdf, http://www.hsaa.ca/index_html/hsaa_successfully_lobbies_ahs_for_improvements_to_insulin_pump_coverage, http://www.asebp.ab.ca/plan_design_changes.html?PF=1).

Experts' responses indicate that in Alberta patients do not need a prescription for IPT and training in IPT is provided by specialized teams associated with diabetes centres and by other healthcare providers who are not diabetes specialists. Manufacturers' responses indicate that they provide

education and training related to IPT for healthcare providers with various backgrounds (including physicians, nurses, dietitians, and pharmacists) in Alberta as well as advanced and ongoing training for certified pump trainers. To become certified pump trainers, the interested healthcare providers have to have their certified diabetes educator designation or equivalent and must successfully complete a training program (that includes hands-on IPT training by the manufacturer's clinical specialist and performance of patient training under observation of the manufacturer's clinical specialist) and an examination.

Currently patients with T1DM may access IPT through diabetes centres or programs or through diabetes education centres or programs located within certain clinics and hospitals across Alberta, which have specific selection criteria and can directly provide IPT initiation and training by a certified pump trainer. Access to these centres and waiting list times are variable and depend on the priority IPT initiation takes in these centres, the number of patients served, and the availability of staff. Patients can also be trained by certified pump trainers working on contract independently of a diabetes education centre.

The literature search conducted for this analysis did not reveal any published reports on the appropriate provision of IPT in Alberta. However, the search results identified a survey conducted in 2003 by the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), which explored the opinions on current practice and IPT service organization by healthcare providers from Quebec.[8] Professionals from four adult care settings and three pediatric care settings who had experience with IPT and who were referred to them by Diabète Québec were interviewed. Results from this survey indicated some organizational problems that needed to be corrected and a number of preconditions that should be met before an IPT access program can be instituted:

- ***Availability of a trained multidisciplinary team:*** Given the limited availability of the current resources, the interviewed healthcare professionals proposed consolidation of IPT services at a few centres only. They identified the need for standardizing the education and training for IPT, which varied from one setting to another. A physician and a nurse were generally involved in training, together with a dietitian at some locations. The manufacturer's role in education prior to IPT use varied, and some wondered if it was ethical to leave education to the companies with no quality control and what the medical liability was in such cases. Representatives from all care settings that participated in the survey agreed that little or no training on IPT was provided to health professionals and that most often it was a question of self-teaching out of personal interest, and the teaching materials were available in English only. The respondents suggested that training prior to pump use be provided only by a person with sufficient practice volume, who could thus develop leading-edge expertise and devote the necessary effort and skills to continuing education. A number of the participating settings have an on-call system in endocrinology, where all the physicians know how to correct insulin dose adjustment problems with the pump.
- ***Patient selection:*** All the care settings participating in the survey identified the need for specific pump prescription and coverage criteria but feared that these clinical criteria would be difficult to apply in practice. Among the patient selection criteria mentioned by the interviewed health professionals, coverage by private insurance was the main criterion in Quebec. The percentage of patients and the clienteles that would benefit from IPT, even if there were no financial obstacles, varied enormously according to the respondents' practice setting and clientele. In adult care settings some considered the pump was providing benefit

only in very rare cases, others in 5%, 20%, or even 50% of their clientele. In pediatric care settings respondents estimated that 30% to 75% of patients would benefit from IPT.

- ***Very clear pump access modalities:*** Survey respondents identified the need for special, limited prescribing, even if it would involve more procedures; determination of a specific number of pumps to be available per clinical setting in proportion to the patient population; and a trial period for which a pump is loaned.
- ***A full range of clinical services:*** As a general rule, IPT was initiated at an outpatient clinic for adult cases and at a day hospital in the case of children. In pediatric settings the interviewed healthcare providers emphasized the importance for a social worker and a psychologist to evaluate the family and school situation. The importance of resources in terms of physician and nursing time devoted to postinstallation follow-up were also emphasized. The follow-up generally requires daily contact between the patient and the care team. Contact gradually diminishes from daily to weekly after 4 to 6 weeks. Based on the experience of most of the care settings, in the long run pump-treated patients become more independent and can adjust doses and boluses on their own. One physician estimated the need for education and nursing support at about 2 or 3 days a week for 40 to 60 adult patients. At the time when the survey was conducted, the manufacturers had a 24-hour, toll-free line, in English only, for anything that had to do with technical problems, and follow-up service was provided by representatives who covered the entire province of Quebec.
- ***Fair access in the regions:*** For usual diabetes follow-up, patients in the regions should have access to a local endocrinologist or to a diabetes nurse at a local day centre. It was felt by some of the interviewed healthcare providers that this could be difficult to organize. One care setting proposed that traveling teams be set up to guarantee access across the province.
- ***Anticipation of the impact on other activities in the health-care system:*** When, in an emergency situation, a patient on IPT consults outside his or her usual care setting, this can pose a problem. For children in daycare centres or at schools, there is a need to provide relevant information, education, and training to the other individuals who look after the child during the day. At the time when the survey was conducted, this task was usually performed by hospital personnel.

An analysis of the case series of the Hospital for Sick Children in Toronto showed the need to elaborate a specific program to follow up with patients using IPT.[92] The results suggest that adherence to treatment regimen and the care in calculating the doses, carbohydrate counting, and observance of boli should be monitored by a program providing multiprofessional support aimed specifically at patients using IPT.

Demand for IPT

Use and demand of IPT in the world

The use of IPT varies worldwide and has been growing steadily, mainly in the United States and Europe, during the past 15 years or so.[1,5,73,76,78,80,90,93-95] It is estimated that IPT is used by about 8% to 15% of individuals with T1DM aged greater than 12 years whereas the rates of IPT use for those aged less than 12 years vary from 15% to 50%.[5,72] Estimates (based on manufacturer data) published in 2006 suggest that more than 270,000 individuals in the United States and more than 180,000 in Europe were treated with IPT in 2005.[80] There are some high-use countries (such as the United States, Israel, and Germany, where between 15% and 25% of T1DM patients use IPT), medium-use

countries (such as France, Sweden, Norway, and the Netherlands, where around 10% of T1DM patients use IPT), and notable low-use countries (such as the United Kingdom and Denmark, where about 1% of T1DM use IPT).

Availability of financial coverage appeared to make the difference between high-use and very low-use countries, as the IPT cost was covered in some countries (United States, Sweden, and the Netherlands) and not covered in others (United Kingdom and Denmark).[1,80] Other probable reasons for this variation include the availability of healthcare professionals trained and certified to initiate IPT services and monitor its use, and a lack of knowledge on what subgroup of individuals with T1DM would benefit the most from and should be using IPT.[1,5,76,78,80,90,93]

Selecting the individuals with T1DM who would most benefit from IPT continues to be a challenge for the healthcare provider trying to determine what patients should be offered IPT on clinical grounds alone.[3-7,34,36,44,61,62,66,72,76,78,90,93,96] There is evidence that the change in A1C upon conversion from MDI to IPT depends upon the baseline level achieved on MDI and that IPT is most effective in most poorly controlled patients.[34,36,44,62,72,93,96] Recently it has been argued that the subgroup best treated by IPT, or who should be offered a trial of IPT, can be derived from an estimate of the effectiveness of this therapy compared with the best MDI regimen for particular clinical problems in T1DM.[93] There are some 5% of individuals with T1DM on MDI with severe, recurrent hypoglycemia. At least another 5% suffer from severe hypoglycemia that is markedly disabling to them. About 15% of MDI users have the syndrome of markedly elevated A1C and wide swings in blood glucose concentration, often with unpredictable, moderate (nonsevere) hypoglycemia. A small percentage would have the dawn phenomenon.

Some of the patients presenting with these clinical problems (which are at least as important in children as they are in adults) are not suitable for IPT because they are unable to perform IPT or are psychologically unsuitable or simply decline IPT and prefer MDI.[8,93] Pickup recently estimated that a minimum target for those individuals with T1DM who should be offered a trial of IPT is about 15% to 20% of cases.[93] This estimate is consistent with some evidence from manufacturers' estimates summarized by the Insulin Pumps Working Group (IPWG) in the United Kingdom suggesting that "new pump starts in high-use countries are slowing, so that a plateau at around 20-25% of people with Type 1 diabetes may be reached".[90] However, further research is needed to better understand the current and the potential future use of IPT.

There has been a wide range of rates of and reasons for IPT discontinuation or dropout in children, adolescents, and adults.[1,8,78,82,83,87] The reported dropout rates vary depending on the studies, and reasons for discontinuation have not been well described in the literature, particularly in children and adolescents. In adult studies subjects who were more likely to discontinue IPT were female, younger, single or divorced, with a shorter duration of diabetes, and who had psychiatric problems. Other reasons to discontinue IPT included not feeling comfortable while wearing IPT devices, lack of improvement in glycemic control, and increased rates of infection. The few studies that have been published recently have reported discontinuation rates up to 26% for insulin pumps.[82,83,87] However, these studies reported discontinuation rates for various insulin pumps that were in use between 1999 and end of 2005. Manufacturers' responses suggest an overall discontinuation rate of up to 10%.

Use and demand of IPT in Canada and in Alberta

The literature search conducted for this analysis did not reveal any published information on usage of IPT in Canada and/or Alberta. Neither did the search results identify any published or publicly accessible Canadian or provincial pump registry, published reports on IPT or MDI practice in Alberta, or any published information on demand for IPT in Canada or in Alberta.

Manufacturer data suggest that approximately 3100 insulin pumps are sold in Canada every year and that 195 Alberta residents with T1DM are "potentially eligible" to purchase insulin pumps every year (Disetronic Medical Systems Inc., Roche Diagnostics, personal communication, 1 September 2009). The current demand for IPT in Canada is estimated to be between 8% and 15% for the population with T1DM (Medtronic of Canada, personal communication, 31 August 2009). The demand rate varies regionally and depends on factors such as patients' access to qualified healthcare professionals and certified pump trainers, reimbursement levels to access insurance funds (public or private), and program delivery models.

It has been estimated that currently there are 11,000 to 18,000 insulin pump users in Canada and 700 to 950 insulin pump users in Alberta (200 to 250 children and adolescents aged 0 to 18 years, and 500 to 700 adults, over 18 years of age) (Medtronic of Canada, personal communication, 31 August and 17 September 2009; Disetronic Medical Systems, Roche Diagnostics, personal communication, 1 September 2009). More than 10,000 individuals currently use insulin pumps manufactured by Medtronic, which also has more than 80% of the market share in Alberta (which means that at least 560 to 760 of the insulin pumps used by Albertans are manufactured by Medtronic).

Approximately 375 of the pump users in Canada and 40 of those in Alberta currently use ACCU-CHECK Spirit insulin pumps manufactured by Disetronic, which projected in 2009 to sell 100 more pumps in Canada and 10 more pumps in Alberta (Disetronic Medical Systems, Roche Diagnostics, personal communication, 1 September 2009).

New pumps are expected to be placed on the market approximately every 4 years because most payers will not be reimbursed for a new unit unless the pump is no longer functional (after the warranty period expires, which is typically after 4 years) or a different model better meets the changing needs of the patient (LifeScan Canada, Animas Canada, personal communication, 28 October 2009; Medtronic of Canada, personal communication, 31 August and 17 September 2009).

The discontinuation rate for IPT in Canada is estimated between 5% and 10% (Medtronic of Canada, personal communication, 31 August and 17 September 2009; Disetronic Medical Systems, Roche Diagnostics, personal communication, 1 September 2009).

Relying on certain assumptions and its experience in the United States, Disetronic Medical Systems roughly estimated the following numbers for potential pump users in Canada and in Alberta (Disetronic Medical Systems, Roche Diagnostics, personal communication, 1 September 2009):

- Assuming a total number of 200,000 Canadian residents with T1DM and a penetration rate of 30% for IPT, it is estimated that there are 60,000 potential insulin pump users in Canada.
- Assuming a total number of 14,285 Albertans with T1DM and a penetration rate of 30% for IPT, it is estimated that there are 4285 potential insulin pump users in Alberta.

Health System Capacity in Alberta

The Insulin Pumps Working Group (IPWG) in the United Kingdom identified a number of factors that should be considered when planning an IPT service.[90] These include user involvement, needs assessment, service planning, paying for pump services, service specification and a best practice model, the role of diabetes networks, and audit.

The establishment of a facility specifically developed for dealing with patients treated by insulin pumps has been identified as an important prerequisite for providing high-quality IPT service.[8,44,75,84,90,92] IPT initiation, follow-up, and management of IPT users require:

- a multidisciplinary team that must include at least a qualified and registered endocrinologist or diabetologist who has in addition been trained in IPT usage, or a practitioner who has an established interest in T1DM and because of his or her expertise is referred such patients by peers and colleagues, and who has been trained in IPT usage; an accredited diabetes educator trained and certified in pump training, usage, and follow-up; and the availability of a registered dietician who understands IPT usage and can advise regarding carbohydrate-counting techniques;
- the provision of a 24-hour emergency number or hotline staffed by a healthcare provider who understands IPT and is trained in its use and who can provide medical and technical counselling 24 hours a day throughout the year;
- the setting and ability to fully train and educate the patient (and family) in IPT usage;
- a signed contract detailing the required standard of care and the provision of data for peer review;
- the entry and maintenance of all patients into the insulin pump register; and
- attendance at an annual update course on IPT.

As identified in the report by the IPWG,[90] a high-quality IPT service needs to:

- be effective and efficient;
- be responsive to the needs of individuals with T1DM, their parents or family, and carers;
- provide treatment and care based on best practice as defined in evidence-based clinical practice guidelines on T1DM;
- deliver the required capacity by providing IPT for everyone who meets the selection criteria as established by best practice;
- be integrated with other elements of care and services for individuals with T1DM;
- define agreed criteria for referral, local protocols, and the care pathway for T1DM;
- be patient centred and provide equitable access, ensuring that patients are treated with dignity and respect, are fully informed about their care, and are able to make decisions about their care in partnership with healthcare professionals;
- audit the provision of IPT service; and
- monitor the number of individuals with T1DM on IPT.

Policy decision makers may wish to consider delivering an IPT service using a model of shared care between a hospital physician with a specialist interest in insulin pumps and a diabetes specialist nurse.[90] The service could be based in the community or the hospital and should consider how to provide 24-hour patient access to clinical and technical support. Decision makers need to consider how best to provide an efficient model to deliver services, which may include networks of care across a geographical area. Local stakeholders, including local education authorities, IPT users, and their caregivers, should be involved in determining what is needed from an IPT service in order to meet local needs.

The literature search conducted for this analysis did not reveal any published reports on workforce capacity for providing IPT service in Alberta. Of the three manufacturers contacted, only Medtronic

of Canada provided information on the distribution of certified pump trainers and healthcare providers capable of initiating and providing IPT services and monitoring their use in Alberta.

Currently Medtronic employs more than 10 diabetes clinical specialists in Canada, who are responsible for liaising with other healthcare professionals regarding their training and education related to IPT and for ensuring that the standards of training are taught, coached, and followed up with the certified pump trainers (Medtronic of Canada, personal communication, 31 August and 17 September 2009). In Alberta there is one Medtronic diabetes clinical specialist, a nurse, who is available to complete pump training in certain circumstances and is also responsible to certify new pump trainers. There are also 24 Medtronic certified pump trainers in Alberta:

- *Medicine Hat:* two nurses at the diabetes education centre within the Medicine Hat Regional Hospital
- *Lethbridge:* one nurse at the diabetes education centre within the Lethbridge Regional Hospital and one pharmacist working under contract independently of a diabetes education centre
- *Calgary:*
    - for adults: three nurses and one dietitian at the diabetes education centre located on Richmond Road in Calgary and three nurses and one pharmacist working on contract independently of a diabetes education centre
    - for pediatrics: two nurses at the diabetes education centre within the Alberta Children's Hospital
- *Red Deer:* three nurses at the diabetes education centre within the Red Deer Regional Hospital Diabetes Education Centre
- *Edmonton:*
    - for adults: three nurses at the University of Alberta Metabolic Clinic and one nurse at the diabetes education centre within the Grey Nuns Hospital
    - for pediatrics: two nurses at the Stollery Children's Hospital
- *Fort McMurray:* one nurse at the diabetes education centre within the Regional Hospital
- *Grande Prairie:* one nurse at the diabetes education centre

In Canada there are approximately 94 pump centres with employees who have been certified on the IPT system manufactured by Disetronic, and 13 of these are in Alberta (Disetronic Medical Systems, Roche Diagnostics, personal communication, 1 September 2009). It is currently estimated that 134 individual pump trainers have been certified on the ACCU-CHEK Spirit insulin pump system in Canada (including contracted and certified trainers). There are 29 contracted individual pump trainers, including contracted pump centres with employees in Canada. Five of these are located in Alberta and are available to provide training throughout the entire province of Alberta.

Limitations

The present review has several limitations. The literature review was limited to published reports of articles and documents that were written in English. Proprietary reports were excluded. Only full-text articles were included because abstracts provide insufficient details to allow an accurate,

unbiased assessment and comparison of the study results. The authors of the abstract-only publications were not contacted for full details of their studies.

Qualitative research literature, which reports patients' and providers' perspectives on the use of MDI and on the use of IPT, was not included.

The present review only summarizes the recommendations from reports of relevant clinical practice guidelines and consensus statements and does not appraise their scientific foundations.

Clear answers could not be provided for some questions due to the absence of relevant data for Alberta. Because of the tight timelines, only several diabetes centres were contacted to determine the number of MDI and IPT users in these centres.

Summary

The social and systems demographics review summarizes the available evidence from the scientific literature in Canada and worldwide and Canadian databases to address the questions about the burden of illness of T1DM, the population dynamics of affected individuals, the current patterns of care, and issues related to the implementation of IPT. The following key findings are highlighted.

Overview of T1DM

- T1DM is a lifelong condition in which both morbidity and treatment affect quality of life, and it places a heavy burden on the affected individual, the family, the healthcare system, and society in terms of both nonmonetary and monetary elements.
- T1DM is a chronic metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action, or both. It encompasses cases that are primarily the result of pancreatic beta cell destruction.
- T1DM is mostly an autoimmune disorder that is likely caused by a complex interaction of both genetic and environmental factors. Its onset is often sudden, and clinical presentation can vary from non-emergency symptoms to severe dehydration, shock, DKA, or diabetic coma.
- If uncontrolled or poorly controlled, T1DM can cause life-threatening acute and chronic complications that are related to the disease itself, to its treatment, or to both.

Epidemiology and population dynamics of affected individuals

- Although T1DM usually accounts for only a minority of the total burden of diabetes in a population (approximately 10%), it is the most predominant form of the disease in younger age groups in most developed countries. It can develop at any age but usually appears in childhood or adolescence. Males and females tend to be equally vulnerable.
- Potential risk factors for T1DM include having a parent with T1DM, early exposure to viruses and toxins, reduced exposure to ultraviolet light, lower vitamin D levels, and early exposure to some nutritional factors.
- The incidence and prevalence rates of T1DM vary according to age, gender, and ethnicity, and large variations are observed among and within countries.
- Worldwide the incidence rate of T1DM has been increasing steadily during the recent decades. T1DM incidence is increasing at a noticeable rate in children (approximately 70,000 children develop T1DM annually at a rate of approximately 3% per year), and there is

evidence indicating a shift to a younger age of onset. The cause of this rise is unknown, but epidemiological studies suggest the involvement of some environmental factors.

- Increases in T1DM incidence in North America are similar to those observed in other parts of the world.
  - Annually, over 15,000 youth (0 to 19 years of age) in the United States are newly diagnosed with T1DM, with an incidence rate of 19.0 per 100,000 per year. Overall, across all ethnic groups and sex, the highest rates of T1DM were observed among 5- to 9-year-old and 10- to 14-year-old youth.
  - Over 240,000 Canadians live with T1DM. In 2007, the estimated number of prevalent cases of T1DM among Canadian youth (0 to 14 years) was 8400. The incidence rate for this age group was estimated at 21.7 per 100,000 cases per year. The estimated incidence rate increased with age from 14.7 for 0- to 4-year-olds, to 24.0 for 5- to 9-year-olds and 26.3 for 10-to 14-year-olds.
  - Childhood T1DM is of particular importance in the Canadian province of Newfoundland and Labrador, where the incidence has been found to be the highest in North America and one of the highest in the world. T1DM incidence in children (0 to 14 years) over the period 1987 to 2005 was 35.08 per 100,000 cases per year, which increased linearly at the rate of 0.78 per 100,000 cases per year.
  - Data from Alberta Health and Wellness suggest that currently T1DM represents more than 13% of all diabetes cases, and the number of cases increased across all age groups between 2006 and 2008.

Patterns of care

- Intensive management of T1DM, including intensive insulin therapy delivered by MDI, is the accepted standard of care for achieving and maintaining near-normal blood glucose in order to reduce risk of complications. However, despite recent advances in intensive insulin therapy, fear of inducing hypoglycemia remains a major barrier in achieving optimal glycemic control safely in all age groups.
- Obtaining and maintaining optimal glycemic control with intensive insulin therapy while striving to minimize the risk of acute complications demands dedication, motivation, energy, knowledge, and continued education from the affected individuals, their family, caregivers, and healthcare providers. For children and adolescents with T1DM, some physiological and developmental issues as well as medical issues may affect their compliance with the prescribed regimen, which may, in turn, lead to poor glycemic control.
- Even the most complex and advanced intensive insulin regimens delivered by MDI cannot account for all the conditions that influence blood glucose levels, and it appears that after a period of attempting to improve control with MDI, at least 15% of individuals with T1DM are markedly uncontrolled, with either an elevated A1C level or glycemic variability or both. Even though an MDI regimen coupled with frequent blood glucose monitoring and accurate carbohydrate counting allows flexibility in meal times and amounts, the number of insulin injections required may be a barrier to good control.

- Guidelines for intensive insulin therapy of T1DM recommend an individualized, intensive insulin regimen using either MDI or IPT as part of an intensive diabetes management. IPT is usually considered after MDI has been tried and failed in optimizing glycemic control safely.
- Both MDI and IPT are available as intensive insulin therapy in Alberta, and according to Alberta experts, most individuals with T1DM are MDI users (approximately 12% of youth and 13% of adults are IPT users).

Implementing IPT as an intensive insulin delivery method

IPT must not be considered as an "easy way out". For it to be successful, IPT requires particular management of patients, patient training, and follow-up within a care framework suitably equipped and run to take account of the technological particularities of this technology, its associated risks, the necessary change in lifestyle, and its cost. The key components of a high-quality IPT service are identifying individuals with T1DM suitable for IPT, ensuring appropriate composition of the specialist team, and monitoring and supporting IPT users.

Patient selection

- Selecting the appropriate individuals with T1DM who would benefit from IPT continues to be a challenge for the health care provider trying to determine what patients should be offered this technology on clinical grounds alone, leaving aside the legitimate issues of patient preference and restrictions due to availability of funding and staffing.
- It is estimated that less than 20% of all individuals with T1DM would most benefit from IPT. It appears that the best candidates would be those who are poorly controlled MDI users, provided that they or their parents and family (for younger children) are highly motivated, have developed an expertise in managing the condition, are able and willing to be trained and able to operate IPT, have appropriate support, and are up to the challenge of frequent glucose monitoring, carbohydrate counting, and frequent contact with the diabetes care team.

Training and ongoing monitoring and support

- Currently training of patients about IPT and its appropriate use is primarily performed by certified consultant pump trainers such as registered nurses and/or pharmacists certified as diabetes educators. In addition to providing technical instruction to patients on the safe operation of insulin pumps, pump trainers may also provide patient management and follow-up for a short period following training.
- Training of healthcare professionals is currently performed by clinical specialists employed by the pump manufacturer. The manufacturer establishes the requirements for becoming a pump trainer. Pump manufacturers also provide 24-hour technical support, generally limited to handling mechanical problems with the pumps.
- Best practice recommends that IPT be prescribed, initiated, implemented, and followed by a multidisciplinary skilled diabetes team, which should include a physician with a special interest in IPT, a diabetes specialist nurse, and a dietitian. The diabetes team should provide structured education programs and advice on diet, lifestyle, and physical activity appropriate for IPT users as well as monitor the ongoing T1DM management and operation of the pump. Frequent contact between the patient and parents or family and diabetes team is required after initiating IPT. Twenty-four hour access to a diabetes team member is desirable.

Entry into and monitoring through a pump register of all IPT users is also recommended as part of IPT service.

IPT diffusion

The uptake of IPT may be limited by several factors, including:

- the cost of the pumps and related supplies,
- the required number of multiple blood glucose measurements to calibrate and check the system for daily insulin dose adjustment, and
- the long-term acceptance of the bodily attachment to the pump.

Implementation issues

- Implementation of IPT creates additional costs related to the training and education of the patients and healthcare providers in the use of pumps, and ongoing monitoring of the pump use. In the case of young school-aged children, IPT training and education may need to be provided to school personnel on the appropriate insulin dosing and pump troubleshooting.
- Busy physician practices may have difficulty in accommodating the lengthy patient visits required to provide necessary education and training in basic and advanced diabetes education skills, IPT operation, and troubleshooting. Therefore, practitioners must have access to qualified individuals who can provide initial education and training in all aspects of IPT, and ongoing education and follow-up support on a long-term basis.
- Establishing a team of qualified and experienced healthcare providers is a prerequisite component of IPT. If a qualified team is unavailable in some areas, diabetes care delivered via telehealth could overcome this inequity in access to IPT services.

APPENDICES

Appendix S.A: Search Strategy for Social Systems and Demographics (S) Approach to Analysis

The search strategy outlined below was conducted 7 and 8 July 2009. Results were limited to papers published in English between 2004 and 2009. In addition to major electronic databases, relevant library collections, websites of practice guidelines, regulatory agencies, evidence-based resources, and other health technology assessment (HTA) related agency resources were searched.

The search strategy was created and carried out prior to the study selection process.

Medical Subject Headings (MeSH) terms relevant to this topic are Insulin Infusion Systems, Infusion Pumps, and Diabetes Mellitus, Type 1.

Table S.A.1: Search strategy

Database	Edition or date searched	Search terms ††
Core databases		
The Cochrane Library http://www.thecochranelibrary.com		The Cochrane database was not searched as the results from this database were included in the T part of the project. Relevant systematic reviews published by Cochrane are indexed in MEDLINE so should be included in the results anyway.
MEDLINE (OVID interface)	7 July 2009 (1950 to June, week 4, 2009)	1 Insulin Infusion Systems/ 2 infusion pumps/ or infusion pumps, implantable/ 3 (insulin or novorapid or humalog or apidra or humulin$ or novolin or levemir or lantus).mp. 4 exp Infusions, Parenteral/ 5 3 and (2 or 4) 6 Administration, Cutaneous/ 7 exp Insulin/ad [Administration & Dosage] 8 6 and 7 9 (insulin pump$ or insulin infusion$ or CSII).mp. 10 (subcutaneous adj2 insulin).mp. 11 (continuous adj2 insulin).mp. 12 ((closed-loop adj2 control) and (insulin or glucose)).mp. 13 1 or 5 or 8 or 9 or 10 or 11 or 12 14 exp Diabetes Mellitus, Type 1/ 15 diabet$.mp. and type 1.ti,ab. 16 14 or 15 17 13 and 16 18 epidemiologic methods/ or data collection/ or health surveys/ or population surveillance/ or sentinel surveillance/ or health care surveys/ or interviews as topic/ or questionnaires/ or qualitative research/ or incidence/ or prevalence/ 19 (prevalence or incidence).mp. and ep.fs. 20 demography/ or age distribution/ or ethnic groups/ or health status/ or exp population groups/ or "catchment area (health)"/ or socioeconomic factors/ or educational status/ or income/ or poverty/ or social class/ or social conditions/ or exp social environment/

		21 (sociodemographic$ or social demographic$).mp. 22 minority groups/ or jurisprudence/ or duty to warn/ or social environment/ or social support/ 23 health education/ or patient education as topic/ or information dissemination/ or attitude to health/ or health knowledge, attitudes, practice/ 24 exp ethics/ or ethical relativism/ 25 Awareness/ or exp Self Concept/ 26 Fear/ or Panic/ 27 cultural competency/ or cultural characteristics/ or cross-cultural comparison/ or cultural diversity/ or transcultural nursing/ 28 health services accessibility/ 29 "patient acceptance of health care"/ or exp patient compliance/ or patient participation/ 30 (adherence or acceptance or acceptability).ti,ab. 31 (burden adj2 (illness or disease or condition or sickness)).mp. 32 ((cultural or ethnic or psychological or linguistic or economic or socioeconomic or psychosocial or social or policy or financial or lifestyle or emotional or psychological) adj2 (factor$ or barrier$ or consideration$ or implication$ or concern$)).mp. 33 (barrier$ adj3 (implement$ or treat$ or therap$)).mp. 34 ((psychological or psychosocial or emotional or financial or economic or resource or lifestyle) adj2 (benefit$ or effect$ or impact$)).mp. 35 Adaptation, psychological/ 36 Quality of life/ 37 Quality-Adjusted Life Years/ 38 ("quality of life" or quality-adjusted life year$ or QoL or HRQL or HRQoL or QALY).mp. 39 (wellbeing or well-being or quality adjusted survival).mp. 40 Health behavior/ or Treatment refusal/ 41 Personal satisfaction/ or exp Consumer satisfaction/ 42 "Health Services Needs and Demand"/ 43 "Quality of Health Care"/ 44 exp Guideline/ 45 Critical Pathways/ 46 Benchmarking/ 47 (benchmark$ or best practice$).mp. 48 standard of care.mp. 49 exp exercise/ or physical exertion/ 50 exp Population Dynamics/ 51 exp "Analysis of Variance"/ 52 adverse events.mp. 53 or/18-52 54 17 and 53 55 limit 52 to yr="2004 - 2009" 56 limit 55 to English language Additional epidemiology search: 57 Diabetes Mellitus, Type 1/ep [Epidemiology] 58 limit 57 to (English language and yr="1999-Current") 59 exp Canada/

		60 Canada.cp. 61 (Canada or Canadian$ or Alberta or British Columbia or Columbie Britannique).af. 62 (Saskatchewan or Manitoba or Ontario or Quebec or New Brunswick or Nouveau Brunswick).af. 63 (Nova Scotia or Nouvelle Ecosse or Prince Edward Island or Ile du Prince Edward or Newfoundland or Terre Neuve or Labrador or Nunavet or Nun?v?t or NWT or Territories du Nord Ouest or Northwest Territories or Yukon).af. 64 (Canada or Canadian$ or Alberta or British Columbia or Columbie Britannique).in. 65 (Saskatchewan or Manitoba or Ontario or Quebec or New Brunswick or Nouveau Brunswick).in. 66 (Nova Scotia or Nouvelle Ecosse or Prince Edward Island or Ile due Prince Edward or Newfoundland or Labrador or Nunavet or Nun?v?t or NWT or Northwest Territories or Territoires du Nord Ouest or Yukon).in. 67 or/59-66 68 World Health/ 69 67 or 68 70 58 and 69
EMBASE (OVID interface)	7 July 2009 (to Week 24)	1 insulin pump/ 2 infusion system/ or infusion pump/ or continuous infusion/ 3 insulin infusion/ 4 subcutaneous drug administration/ 5 (insulin or novorapid or humalog or apidra or humulin$ or novolin or levemir or lantus).mp. 6 (2 or 4) and 5 7 (subcutaneous adj2 insulin).mp. 8 (continuous adj2 insulin).mp. 9 (insulin pump$ or insulin infusion$ or CSII).mp. 10 ((closed-loop adj2 control) and (insulin or glucose)).mp. 11 1 or 2 or 6 or 7 or 8 or 9 or 10 12 insulin dependent diabetes mellitus/ or juvenile diabetes mellitus/ or lipoatrophic diabetes mellitus/ or pregnancy diabetes mellitus/ or maternal diabetes mellitus/ 13 diabet$.mp. and type 1.ti,ab. 14 12 or 13 15 11 and 14 16 (type 2 not (type 1 and type 2)).ti,ab. 17 15 not 16 18 (prevalence or incidence).mp. 19 demography/ 20 epidemiological data/ or comorbidity/ or geographic distribution/ or age distribution/ or incidence/ or prevalence/ or life expectancy/ or health status/ 21 exp “ethnic or racial aspects”/ 22 exp “ethnic and racial groups”/ or ethnic group/ 23 income/ 24 exp social status/ or exp socioeconomics/ 25 sociodemographic$.mp. 26 minority group/

		27 ethics/ or bioethics/ or medical ethics/ or ethical decision making/ 28 legal aspect/ or law/ or legal liability/ or medical liability/ or patient right/ or jurisprudence/ 29 informed consent/ 30 social support/ 31 exp social environment/ 32 health education/ or health promotion/ or patient education/ 33 information dissemination/ or patient information/ 34 attitude to health/ or cultural bias/ or cultural sensitivity/ or exp patient attitude/ 35 awareness/ 36 health care access/ or health care availability/ or health care distribution/ or health care need/ 37 (burden adj2 (illness or condition or sickness or disease)).mp. 38 ((cultural or ethnic or psychological or linguistic or economic or socioeconomic or psychosocial or social or policy or financial or lifestyle or emotional or psychological) adj2 (factor$ or barrier$ or consideration$ or implication$ or concern$)).mp. 39 (barrier$ adj3 (implement$ or treat$ or therap$)).mp. 40 cultural competence/ 41 transcultural care/ 42 exp "quality of life"/ 43 ("quality of life" or quality-adjusted life year$ or QoL or HRQL or HRQoL or QALY).ti,ab. 44 wellbeing/ 45 (wellbeing or well-being or quality adjusted survival).mp. 46 ((psychological or psychosocial or emotional or financial or economic or resource) adj2 (benefit$ or effect$)).mp. 47 adherence.ti,ab. 48 "analysis of variance"/ 49 qualitative research/ 50 health survey/ 51 exp data collection method/ 52 fear/ or anxiety/ 53 physical activity/ 54 population dynamics/ 55 or/18-54 56 17 and 55 57 limit 56 to yr="2004-Current" 58 limit 57 to English language
CINAHL	7 July 2009	1. ((MH "Infusion Pumps+") OR (MH "Infusions, Subcutaneous") OR (MH "Injections+")) and ((MH "Insulin+") OR (insulin or novorapid or humalog or apidra or humulin$ or novolin or levemir or lantus)) 2. "continuous insulin" or "continuous subcutaneous" or "insulin pump*" or "insulin infusion*" or IPT or CSII 3. 1 or 2 4. (MH "Diabetes Mellitus, Insulin-Dependent") OR (MH "Pregnancy in Diabetes+") OR (diabet* and "type 1") 5. 3 and 4 6. (MH "Quality of Life+") OR (MH "Epidemiology+") OR (MH "Demography+") OR (MH "Health Status+") OR (MH "Ethnic Groups+") OR (MH "Socioeconomic Factors+") OR (MH "Minority Groups") OR (MH

		"Ethics+") OR (MH "Patient Rights+") OR (MH "Psychosocial Aspects of Illness+") OR (MH "Consent+") OR (MH "Access to Information") OR (MH "Diabetes Education") OR (MH "Selective Dissemination of Information") OR (MH "Attitude+") OR (MH "Cultural Competence") OR (MH "Qualitative Studies+") OR (MH "Health Services Accessibility+") OR (MH "Adverse Health Care Event+") OR (MH "Life Style+") OR (MH "Transcultural Care") OR (MH "Wellness") OR (MH "Analysis of Variance+") OR (MH "Physical Activity") OR ("burden of illness" OR "burden of disease" or "burden of sickness" or "burden of condition") OR (MH "Adaptation, Psychological") OR (MH "Anxiety") OR (MH "Fear") OR (MH "Patient Compliance+") OR "quality of life" OR "quality adjusted life year" OR QoL OR HRQL OR HRQoL OR QALY 7. 5 and 6 limit to 2004-2009 8. "type 2" not ("Type 1" AND "type 2") 9. 7 NOT 8
Sociological Abstracts	7 July 2009	"insulin pump" or "insulin pumps" or "insulin infusion" or "insulin infusions" or CSII or IPT or "subcutaneous insulin" limited to 2004-2009 Only 10 results were found, the majority of which were not relevant, as the term IPT in the sociological literature represents such other concepts as international political theory and interpersonal psychotherapy. The results were therefore not imported.
SocIndex	7 July 2009	("insulin pump" or "insulin pumps" or "insulin infusion" or "insulin infusions" or CSII or IPT or "subcutaneous insulin") AND diabet* limited to 2004-2009 Only four references retrieved. Since were duplicates of previously found references, the results were not uploaded to Reference Manager.
Web of Science	7 July 2009	#1 Topic=("insulin pump*" or "insulin infusion*" or CSII or IPT or "subcutaneous insulin") AND Topic=diabet* #2 Topic=("quality of life" or survey* or questionnaire* or prevalence or incidence or epidemiolog* or interview* or qualitative or demography or distribution or socioeconomic*) OR Topic=(education* or income or poverty or social or sociodemographic or attitude* or awareness or access* or barrier* or ethics or fear or anxiety or satisfaction) OR Topic=(acceptance or adherence or compliance or burden or psychological or linguistic or lifestyle or emotion* or psychosocial or financ* or QALY or "quality adjusted life year" or wellbeing) #3 #1 AND #2 Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2004-2009 #4 Topic=("type 2") NOT Topic=("type 1" AND "type 2") #5 #3 NOT #4
Biosis Previews	8 July 2009	#1 Topic=("insulin pump*" or "insulin infusion*" or CSII or IPT or "subcutaneous insulin") AND Topic=diabet* #2 Topic=("quality of life" or survey* or questionnaire* or prevalence or incidence or epidemiolog* or interview* or qualitative or demography or distribution or socioeconomic*) OR Topic=(education* or income or poverty or social or sociodemographic or attitude* or awareness or access* or barrier* or ethics or fear or anxiety or satisfaction) OR Topic=(acceptance or adherence or compliance or burden or psychological or linguistic or lifestyle or emotion* or psychosocial or financ* or QALY or "quality adjusted life year" or wellbeing) #3 #1 AND #2 Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2004-2009 #4 Topic=("type 2") NOT Topic=("type 1" AND "type 2") #5 #3 NOT #4
PubMed	7 July 2009	#8 Search #6 NOT #7 Limits: Publication Date from 2004 to 2009 #7 Search type 2 NOT (type 1 AND type 2)

		#6 Search #4 AND #5 #5 Search quality of life OR survey* OR questionnaire* OR prevalence OR incidence OR epidemiolog* OR interview* OR qualitative OR demography OR distribution OR socioeconomic* OR education* OR income OR poverty OR social OR sociodemographic OR attitude* OR awareness OR access* OR barrier* OR ethics OR fear OR anxiety OR satisfaction OR acceptance OR adherence OR compliance OR burden OR psychological OR linguistic OR lifestyle OR emotion* OR psychosocial OR financ* OR QALY OR quality-adjusted life year OR wellbeing #4 Search #1 AND #2 AND #3 #3 Search in process[sb] OR pubmednotmedline[sb] OR publisher[sb] #2 Search diabet* #1 Search insulin pump* OR insulin infusion* OR CSII OR IPT OR subcutaneous insulin
Guidelines		
CMA infobase (http://www.cma.ca/index.cfm/ci_id/54316/la_id/1.htm)	10 February 2009	Insulin
TOP (http://www.topalbertadoctors.org/cpg.html)	4 March 2009	Browsed list of guidelines; none related to diabetes
National Guidelines Clearinghouse www.guideline.gov/	10 February 2009	"Insulin pump"; "insulin pumps"; "insulin infusion"; "insulin infusions"; CSII
HTA Agencies		
AETMIS (http://www.aetmis.gouv.qc.ca/site/en_publications.phtml)	10 February 2009	Insulin
CADTH (http://www.cadth.ca/index.php/en/hta/reports-publications/search)	10 February 2009	Insulin
Medical Advisory Secretariat http://www.health.gov.on.ca/English/providers/program/mas/mas_mn.html	10 February 2009	Browsed list of publications
NICE http://www.nice.org.uk/	10 February 2009	Insulin infusion*; insulin pump*; CSII
EuroScan http://www.euroscan.org.uk/	10 February 2009	Insulin
Health economics resources		
Centre for Health Economics and Policy Analysis http://www.chepa.org	10 February 2009	Insulin
Centre for Health Economics Research and Evaluation http://datasearch.uts.edu.au/chere/research/SearchPublication.cfm	10 February 2009	Insulin

Library catalogues		
NEOS catalogue	10 February 2009	"Insulin pump"; "insulin pumps"; "insulin infusion"; "insulin infusions"; CSII
Websites		
Canadian Diabetes Association (http://www.diabetes.ca)	4 March 2009	

†† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word; e.g., surg* retrieves surgery, surgical, surgeon, etc. Searches separated by semicolons have been entered separately into the search interface.

REFERENCES

1. *Pharmacotherapy of diabetes: (electronic resource)new developments: improving life and prognosis for diabetic patients*. Mogensen CR, editor. New York: Springer; 2007.
2. Sperling MA, editor. *Type 1 diabetes: etiology and treatment*. Totowa, NJ: Humana Press, 2003.
3. Bangstad HJ. ISPAD clinical practice consensus guidelines 2006-2007: insulin treatment. *Pediatric Diabetes* 2007;8(2):88-102.
4. Eugster EA, Francis G, Lawson-Wilkins Drug and Therapeutics Committee. Position statement: continuous subcutaneous insulin infusion in very young children with type 1 diabetes. *Pediatrics* 2006;118(4):1244-9.
5. Liberatore R Jr, Damiani D. Insulin pump therapy in type 1 diabetes mellitus. *Jornal de Pediatria* 2006;82(4):249-54.
6. Phillip M, Battelino T, Rodriguez H, Danne T, Kaufman F. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2007;30(6):1653-62.
7. Hall AP. Assessment and management of diabetes mellitus. *Foundation Years* 2008;4(6):224-9.
8. Cote B, St-Hilaire C. *Comparison of the insulin pump and multiple daily insulin injections in intensive therapy for type 1 diabetes*. Montreal QC: Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), 2005. Report No.: AETMIS 04-07.
9. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Type 1 diabetes in children and adolescents*. Toronto ON: Canadian Diabetes Association; 2008.
10. American Diabetes Association. Standards of medical care in diabetes: 2009. *Diabetes Care* 2009;32 (Suppl 1):S13-S61.
11. Dejkhamron P. Childhood diabetes mellitus: recent advances and future prospects. *Indian Journal of Medical Research* 2007;125(3):231-50.
12. Australasian Paediatric Endocrine Group for the Department of Health and Ageing. *Clinical practice guidelines: type 1 diabetes in children and adolescents*. Australian Government; 2005.
13. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care* 2005;28(1):186-212.
14. Zipris D. Epidemiology of type 1 diabetes and what animal models teach us about the role of viruses in disease mechanisms. *Clinical Immunology* 2009;131(1):11-23.
15. Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. *BMJ* 2009;328:750-4.
16. Dupre J. Preventive interventions for type 1 diabetes: history, appraisal and prospects. *Canadian Journal of Diabetes* 2007;31(4):384-94.

17. *Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults*. London UK: National Institute for Clinical Excellence (NICE); 2009. Report No.: Clinical Guideline 15.

18. Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, Tuomilehto J, for the Diabetes Mondiale (DiaMond) Project Group. Incidence of childhood type 1 diabetes worldwide. *Diabetes Care* 2000;23(10):1516-26.

19. DiaMond Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. *Diabetes Medicine* 2006;23(8):857-66.

20. Naughton MJ, Ruggiero AM, Lawrence JM, Imperatore G, Klingensmith GJ, Waitzfelder B, et al. Health-related quality of life of children and adolescents with type 1 or type 2 diabetes mellitus: SEARCH for Diabetes in Youth Study. *Archives of Pediatrics & Adolescent Medicine* 2008;162(7):649-57.

21. Muntoni S, Muntoni S. Epidemiological association between some dietary habits and the increasing incidence of type 1 diabetes worldwide. *Annals of Nutrition & Metabolism* 2006;50(1):11-9.

22. Benson VS, Vanleeuwen JA, Taylor J, McKinney PA, Van TL. Food consumption and the risk of type 1 diabetes in children and youth: a population-based, case-control study in Prince Edward Island, Canada. *Journal of the American College of Nutrition* 2008;27(3):414-20.

23. Soltesz G, Patterson CC, Dahlquist G. Worldwide childhood type 1 diabetes incidence: what can we learn from epidemiology? *Pediatric Diabetes* 2007;8(Suppl 6):6-14.

24. Peter S. Trends in the incidence of type I diabetes mellitus worldwide. *West Indian Medical Journal* 2007;56(3):264-9.

25. Smith MJ. National Diabetes Month: diabetes around the world. *Diabetes Self-Management* 2008;25(6):29-34.

26. Newhook LA, Grant M, Sloka S, Hoque M, Paterson AD, Hagerty D, et al. Very high and increasing incidence of type 1 diabetes mellitus in Newfoundland and Labrador, Canada. *Pediatric Diabetes* 2008;9(3 Pt 2):62-8.

27. Newhook LA, Curtis J, Hagerty D, Grant M, Paterson AD, Crummel C, et al. High incidence of childhood type 1 diabetes in the Avalon Peninsula, Newfoundland, Canada. *Diabetes Care* 2004;27(4):885-8.

28. Libman IM, LaPorte RE. Changing trends in epidemiology of type 1 diabetes mellitus throughout the world: how far have we come and where do we go from here? *Pediatric Diabetes* 2005;6(3):119-21.

29. Daneman D. State of the world's children with diabetes. *Pediatric Diabetes* 2009;10(2):120-6.

30. Mohr SB, Garland CF, Gorham ED, Garland FC. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. *Diabetologia* 2008;51(8):1391-8.

31. Sloka S, Grant M, Newhook LA. Time series analysis of ultraviolet B radiation and type 1 diabetes in Newfoundland. *Pediatric Diabetes* 2008;9(2):81-6.

32. Dales R, Chen Y, Lin M, Karsh J. The association between allergy and diabetes in the Canadian population: implications for the Th1-Th2 hypothesis. *European Journal of Epidemiology* 2005;20(8):713-7.

33. Alaghehbandan R, Collins KD, Newhook LA, MacDonald D. Childhood type 1 diabetes mellitus in Newfoundland and Labrador, Canada. *Diabetes Research and Clinical Practice* 2006;74(1):82-9. Erratum in: *Diabetes Research and Clinical Practice* 2007;75(2):252.

34. Varvarovska J. Mastering the treatment of diabetes mellitus type 1 in childhood and adolescence. *Current Pediatric Reviews* 2007;3(2):129-39.

35. Walsh MG, Zgibor J, Songer T, Borch-Johnsen K, Orchard TJ, DiaComp I. The socioeconomic correlates of global complication prevalence in type 1 diabetes (T1D): a multinational comparison. *Diabetes Research and Clinical Practice* 2005;70(2):143-50.

36. Bertuzzi F, Verzaro R, Provenzano V, Ricordi C. Brittle type 1 diabetes mellitus. *Current Medicinal Chemistry* 2007;14(16):1739-44.

37. DeVries JH, Snoek FJ, Heine RJ. Persistent poor glycaemic control in adult type 1 diabetes: a closer look at the problem. *Diabetic Medicine* 2004;21(12):1263-8.

38. Unger J. Management of diabetes in pregnancy, childhood, and adolescence. *Primary Care: Clinics in Office Practice* 2007;34(4):809-43.

39. University of Alberta/Capital Health Evidence-based Practice Center. *Diabetes education for children with type 1 diabetes mellitus and their families.* Rockville MD: Agency for Healthcare Research and Quality (AHRQ); 2008. Report No.: 08-E011.

40. Campbell S, Suebwongpat A, Standfield L, Weston A. Systematic review update and economic evaluation for the New Zealand setting. *HSAC Report* 2008;1(3).

41. World Health Organization (WHO). *Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation.* Geneva, Switzerland: WHO; 2006.

42. Roglic G. Diabetes in women: the global perspective. *International Journal of Gynaecology & Obstetrics* 2009;104(Suppl 1):S11-S13.

43. Reynolds KM. *Comparison of quality of life in diabetics using insulin injection therapy versus subcutaneous insulin infusion therapy.* Ypsilanti: Eastern Michigan University; 2007.

44. National Institute for Health and Clinical Excellence (NICE). *Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus* [Internet]. London: Nice; 2008 July [cited 2009 Sep 30]. Available from: http://www.mims.co.uk/news/882207/Continuous-Subcutaneous-Insulin-Infusion-Treatment-Diabetes-Mellitus/.

45. Murphy HR, Rayman G, Duffield K, Lewis KS, Kelly S, Johal B, et al. Changes in the glycemic profiles of women with type 1 and type 2 diabetes during pregnancy. *Diabetes Care* 2007;30(11):2785-91.

46. Evers IM, ter Braak EWMT, de Valk HW, van der Schoot B, Janssen N, Visser GHA. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care* 2002;25(3):554-9.

47. National Collaborating Centre for Women's and Children's Health. *Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period.* London: National

Institute for Health and Clinical Excellence (NICE); 2008. Report No.: NICE Clinical Guideline 63.

48. Legault L, Polychronakos C. Annual incidence of type 1 diabetes in Quebec between 1989-2000 in children. *Clinical & Investigative Medicine* 2006;29(1):10-3.

49. Nordwall M, Ludvigsson J. Clinical manifestations and beta cell function in Swedish diabetic children have remained unchanged during the last 25 years. *Diabetes: Metabolism Research and* Reviews 2008;24(6):472-9.

50. Silink M. Childhood diabetes: a global perspective. *Hormone Research* 2002;57(Suppl 1):1-5.

51. Gale EAM. The rise of childhood type 1 diabetes in the 20th century. Diabetes [Internet] 2002 Dec 12 [cited 2009 Jul 7];51(12):3353-61. DOI: 10.2337/diabetes.51.12.3353. Available from: *http://www.medscape.com/viewarticle/445672*.

52. Vriesendorp TM, van SS, DeVries JH, de JE, Rosendaal FR, Schultz MJ, et al. Predisposing factors for hypoglycemia in the intensive care unit. *Critical Care Medicine* 2006;34(1):96-101.

53. Writing Group for the SEARCH for Diabetes in Youth Study Group, Dabelea D, Bell RA, D'Agostino RB, Jr., Imperatore G, Johansen JM, et al. Incidence of diabetes in youth in the United States. *JAMA* 2007;297(24):2716-24. Erratum in: *JAMA* 2007;298(6):627.

54. Aanstoot HJ, Anderson BJ, Daneman D, Danne T, Donaghue K, Kaufman F, et al. The global burden of youth diabetes: perspectives and potential. *Pediatric Diabetes* 2007;8(Suppl 8):1-44.

55. Sandhu N, Witmans MB, Lemay JF, Crawford S, Jadavji N, Pacaud D. Prevalence of overweight and obesity in children and adolescents with type 1 diabetes mellitus. *Journal of Pediatric Endocrinology* 2008;21(7):631-40.

56. Public Health Agency of Canada. *Report from the National Diabetes Surveillance System: diabetes in Canada, 2008*. Ottawa ON: Public Health Agency of Canada; 2009.

57. American Diabetes Association. Economic costs of diabetes in the U.S. in 2007. *Diabetes Care* 2008;31(3):596-615.

58. Skyler JS, Diabetes TrialNet Study Group. Update on worldwide efforts to prevent type 1 diabetes. *Annals of the New York Academy of Sciences* 2008;1150:190-6.

59. Guidelines & Protocols Advisory Committee. *Diabetes Care*. Vancouver BC: Ministry of Health; 2005.

60. The International Expert Committee. International expert committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009;32(7):1-8.

61. Desmangles JC. Treatment of type 1 diabetes in children and adolescents. *Drug Development Research* 2008;69(3):158-64.

62. Campbell F. The pros and cons of continuous subcutaneous insulin infusion (CSII) therapy in the paediatric population and practical considerations when choosing and initiating CSII in children. *British Journal of Diabetes and Vascular Disease* 2008;8(Suppl 1):S6-S10.

63. 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 England Journal of Medicine* 1993;329(14):977-86.

64. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *New England Journal of Medicine* 2000;342(6):381-9.

65. Brunton S. Insulin delivery systems: reducing barriers to insulin therapy and advancing diabetes mellitus treatment. *American Journal of Medicine* 2008;121(Suppl 6):S35-S41.

66. Shalitin S, Phillip M. The use of insulin pump therapy in the pediatric age group. *Hormone Research* 2008;70(1):14-21.

67. Hilliard ME, Goeke-Morey M, Cogen FR, Henderson C, Streisand R. Predictors of diabetes-related quality of life after transitioning to the insulin pump. *Journal of Pediatric Psychology* 2009;34(2):137-46.

68. Valenzuela JM, Patino AM, McCullough J, Ring C, Sanchez J, Eidson M, et al. Insulin pump therapy and health-related quality of life in children and adolescents with type 1 diabetes. *Journal of Pediatric Psychology* 2006;31(6):650-60.

69. Weissberg-Benchell J, Goodman SS, Antisdel Lomaglio J, Zebracki K. The use of continuous subcutaneous insulin infusion (CSII): parental and professional perceptions of self-care mastery and autonomy in children and adolescents. *Journal of Pediatric Psychology* 2007;32(10):1196-202.

70. Cobry E. C. Use of CoZmonitor in youth with type 1 diabetes. *Pediatric Diabetes* 2008;9(2):148-51.

71. Greening L, Stoppelbein L, Konishi C, Sytsma Jordan S, Moll G. Child routines and youths' adherence to treatment for type 1 diabetes. *Journal of Pediatric Psychology* 2007;32(4):437-47.

72. Pickup JC. NICE guidance on continuous subcutaneous insulin infusion 2008: review of the technology appraisal guidance. *Diabetic Medicine* 2009;26(1):1-4.

73. Paris CA, Imperatore G, Klingensmith G, Petitti D, Rodriguez B, Anderson AM, et al. Predictors of insulin regimens and impact on outcomes in youth with type 1 diabetes: the SEARCH for Diabetes in Youth Study. *Journal of Pediatrics* 200955(2):61-2.

74. Potti LG, Haines ST. Continuous subcutaneous insulin infusion therapy: a primer on insulin pumps. *Journal of the American Pharmaceutical Association* 2009;49(1):e1-e13.

75. Boyd LC. Insulin pump therapy training and management: an opportunity for community pharmacists. *Journal of Managed Care Pharmacy* 2008;14(8):790-4.

76. Skyler JS, Ponder S, Kruger DF, Matheson D, Parkin CG. Is there a place for insulin pump therapy in your practice? *Clinical Diabetes* 2007;25(2):50-6.

77. Diabetes UK. *Position statement: insulin pump therapy also known as continuous subcutaneous insulin infusion (CSII)*. London: Diabetes UK; 2006 Dec [cited 2009 Jan 19]. Available from: *http://www.diabetes.org.uk/About_us/Our-Views/Position_statements/Insulin_pump_therapy*.

78. Schade DS, Valentine V. Are insulin pumps underutilized in type 1 diabetes? No. *Diabetes Care* 2006;29(6):1453-5.

79. Ludvigsson J, Samuelsson U. Continuous insulin infusion (CSII) or modern type of multiple daily injections (MDI) in diabetic children and adolescents a critical review on a controversial issue. *Pediatric Endocrinology Reviews* 2007;5(2):666-78.

80. Selam JL. CSII in Europe: where are we, where are we going? An analysis of articles published in Infusystems International. *Diabetes Research and Clinical Practice* 2006;74(Suppl 2):S123-S126.

81. Hammond P, Liebl A, Grunder S. International survey of insulin pump users: Impact of continuous subcutaneous insulin infusion therapy on glucose control and quality of life. *Primary Care Diabetes* 2007;1(3):143-6.

82. Wood JR, Moreland EC, Volkening LK, Svoren BM, Butler DA, Laffel LM. Durability of insulin pump use in pediatric patients with type 1 diabetes. *Diabetes Care* 2006;29(11):2355-60.

83. Ronsin O, Jannot-Lamotte MF, Vague P, Lassman-Vague V. Factors related to CSII compliance. *Diabetes & Metabolism* 2005;31(1):90-5.

84. Dartford and Gravesham NHS. *Insulin pump therapy (CSII) in children.* Dartford, UK: Dartford and Gravesham NHS; 2007 Aug. 12 p. Report No: PEAD S005.

85. Low KG, Massa L, Lehman D, Olshan JS. Insulin pump use in young adolescents with type 1 diabetes: a descriptive study. *Pediatric Diabetes* 2005;6(1):22-31.

86. Scheidegger U, Allemann S, Scheidegger K, Diem P. Continuous subcutaneous insulin infusion therapy: effects on quality of life. *Swiss Medical Weekly* 2007;137(33-34):476-82.

87. Babar GS. Factors associated with adherence to continuous subcutaneous insulin infusion in pediatric diabetes. *Diabetes Technology and Therapeutics* 2009;11(3):131-7.

88. Barnard KD, Lloyd CE, Skinner TC. Systematic literature review: quality of life associated with insulin pump use in type 1 diabetes. *Diabetic Medicine* 2007;24(6):607-17.

89. Aberle I, Scholz U, Bach-Kliegel B, Fischer C, Gorny M, Langer K, et al. Psychological aspects in continuous subcutaneous insulin infusion: a retrospective study. *Journal of Psychology* 2009;143(2):147-60.

90. Insulin Pumps Working Group. *Insulin pump services.* London: Department of Health; 2007.

91. Ontario Ministry of Health and Long-Term Care, Assistive Devices Program (ADP). *Administration manual for the insulin pump and supplies program. Section 1: policies and procedures.* Ottawa ON; 2008 Sep.

92. Liberatore R Jr., Pearlman K, Buccino J, Artiles-Sisk A, Daneman D. Continuous subcutaneous insulin infusion pump treatment in children with type 1 diabetes mellitus. *Journal of Pediatric Endocrinology & Metabolism* 2004;17:223-6.

93. Pickup JC. Are insulin pumps underutilized in type 1 diabetes? Yes. *Diabetes Care* 2006;29(6):1449-52.

94. Selam JL. Insulin pumps in Europe. *Infusystems* 2005;4-19.

95. Jankovec Z, Krcma M, Lacigova S, Zourek M, Rusavy Z. National registry of patients treated with continuous subcutaneous insulin infusion (CSII) in the Czech Republic: long-term results. *Infusystems* 2005;4:421-4.

96. Currie CJ. Reliably assessing the cost-effectiveness of continuous subcutaneous insulin infusion vs. multiple daily injections in the UK: what are the issues? *Diabetes Medicine* 2007;24(10):1058-9.

SECTION TWO: SAFETY AND EFFICACY OF INSULIN PUMP THERAPY (T)

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Introduction

Purpose of assessment

To determine the potential role of IPT in the treatment of patients with T1DM in Alberta compared to MDI using pen or syringe.

Objective

To perform a systematic review and critical appraisal of currently best available research evidence on the safety and efficacy or effectiveness of IPT compared to MDI for the treatment of patients with T1DM.

Research questions

The Technology (T) section of the report attempts to address the following questions:

- Is IPT safe compared to MDI in terms of complications and side effects for the treatment of patients with T1DM?
- Is IPT effective compared to MDI in terms of short-, intermediate-, and long-term outcomes (glycemic control, quality of life, secondary complications of diabetes) in the treatment of patients with T1DM?
- What subpopulation might benefit from IPT compared to MDI?
- What are the established criteria for initiating IPT?

The scope of the Technology section of the report was defined as follows.

Population: all patients with T1DM, categorized into the following four groups of interest (age category defined by the Public Health Agency of Canada):

- **Adults:** 19 years or older
- **Preschool children:** 0 to 6 years
- **Children and adolescents:** 7 to 18 years
- **Pregnant women**

Intervention: all currently used external insulin pumps regardless of approval status by Health Canada or the United States Food and Drug Administration (FDA).

Comparator: MDI (defined as three or more daily insulin injections) using pens or syringes.

Outcomes: safety outcomes, including adverse events (diabetic ketoacidosis, severe hypoglycemia) or complications (infections, pump malfunction); efficacy and effectiveness outcomes include glycemic control (e.g., glycosylated hemoglobin), patient satisfaction and quality of life, and secondary complications of diabetes, neuro-cognitive function and behaviour changes in children if applicable, and pregnancy outcomes if applicable.

Description of technology

Insulin pump therapy (IPT), also known as continuous subcutaneous insulin infusion (CSII), attempts to mimic the complex mechanism of insulin secretion by the pancreas as closely as technologically possible.[1,2] Although the term *CSII* appears to be used most frequently in the literature, *insulin pump therapy (IPT)* will be used throughout this report as this is the preferred term.

Insulin pumps

Definition

An insulin pump is a complex electronic device that delivers insulin from a small cartridge (or syringe) filled with insulin.[3] Most insulin pumps deliver insulin through an infusion set consisting of a plastic tube connected to a small cannula that is placed in subcutaneous tissue, usually in the abdominal region. The upper arms, thighs, and hips or upper buttocks can also be used as infusion sites.[1,3]

Features

Insulin pumps are computerized devices that allow patients to program, temporarily adjust, or suspend insulin infusion rates as well as deliver precise doses.[1] They are designed to be small, light, and battery powered as they are worn continuously by the patient.[3] Notable features available in different pumps include:[2]

- small incremental changes (0.025 or 0.05 unit) in basal rates, important when the total daily insulin dose is low (e.g., for infants and toddlers);
- automatic calculation of correction boluses based on insulin-to-carbohydrate ratios and insulin sensitivity factors;
- direct communication with a blood glucose meter, which can assist with bolus dose calculation;
- alarm features that can remind a child if a meal bolus is missed; and
- a pump memory able to review insulin bolus, carbohydrate intake used in bolus calculations, and blood glucose levels, which can be most useful in the counselling of patients regarding their diabetes management.

All pumps have alarms to alert users to situations that could compromise insulin delivery, such as battery depletion, an empty insulin cartridge, or a blocked cannula. Additional warnings can be generated by some pumps when blood glucose levels entered by the user (or transmitted from a blood glucose monitor) fall outside preset limits. Options to set customized reminders and warnings are also available. Alarms and reminders are given by audible beeps, vibration, or both.[3]

The features of some newest models of insulin pumps approved by Health Canada are outlined in Table T.1.

Table T.1: Features of insulin pumps from three major manufacturers[a]

	ACCU-CHEK Spirit	Animas 2020	MiniMed Paradigm 522/722
Manufacturer	Desetronic Medical Systems	Animas Canada	Medtronic of Canada
Size (inches)	3.2 × 2.2 × 0.8	3 × 2 × 0.86	2.0 × 3.0 × 0.8 (model 522), 2.0 × 3.6 × 0.8 (model 722)
Weight (ounces)	4.0 with battery and full cartridge	3.13 with battery and full cartridge	3.53 (model 522), 3.81 (model 722)
Warranty (yr)	4	4	4
Reservoir size (U)	315	200	176 (model 522), 176 or 300 (model 722)
Infusion set connection	Luer-lock	Luer-lock	Proprietary
Battery	One AA alkaline	One AA lithium or alkaline	One AAA alkaline
Basal profiles	Store up to 5 profiles with up to 24 rates each	Store up to 4 profiles with up to 12 rates each	Store up to 3 profiles with up to 48 rates each
Basal delivery (U/h)	Range from 0.1 to 25	Range from 0.025 to 25	Range from 0.05 to 35
Smallest increment (U)	0.1	0.025	0.05
Temporary basal delivery	10% increments from 0% to 200% based on baseline basal rate delivered in 15-min intervals over 15 min to 24 h	10% increments based on baseline basal rate delivered in 30-min intervals over 30 min to 24 h	Percentage change from baseline or by units/h in 30-min intervals over 30 min to 24 h
Tracks bolus on board	No	Yes	Yes
Memory	Stores up to the last 30 boluses, 30 alarms and errors, 30 TDDs, 30 temporary basal rate increases/decreases	Stores up to the last 500 boluses,120 TDDs, 30 alarms, 60 primes, 30 suspends, and 270 basal records	Stores up to 90 days of data
Waterproof	Up to 1 h	Up to 24 h at 12 ft	Water resistant
Download/ available software	Uses ACCU-CHEK Compass software with PDA Smartphone that come with Bolus calculator, infrared port for wireless data transfer	Uses ezManager to download pump information to PC, infrared port for wireless data transfer	Uses CareLink, a free Web-based download software
Other features	Bright backlight display, audible or vibrating alerts, available in 12 languages, side-mounted tactile buttons, menu navigation simplified with texts and icons, pump "skins" to personalize look of the pump, multiple safety alarms	Large flat-panel screen with high-contrast colour, has ezCarb in-pump food database that stores up to 500 food items, personalize audio notifications or vibrate for pump alarms, pump comes in multiple colours	Paradigm Real-time glucose-monitoring system measuring blood glucose every 1 min reporting an average every 5 min, large font on display, hypoglycemia prevention alarms, bolus wizard calculator, beep/vibrate alerts, four colours available

[a]Source: modified from Potti and Haines 2009[1]

Abbreviations: ft: feet; h: hour; min: minute; PC: personal computer; PDA: personal digital assistant; TDD: total daily dose; U: unit; yr: year

The first insulin pump was available in the late 1970s but proved to be problematic.[2] Ongoing development of smaller, more efficient, and user-friendly pumps in the past few decades have resulted in the insulin pumps closely mimicking the physiological method of insulin delivery.[2,4]

Advanced pump features include multiple basal rates, fine adjustment of basal rates, smaller pumps and better infusion sets, greater safety and reliability, wireless link to a glucose meter, bolus calculator (taking into account the patient's current blood glucose level, insulin sensitivity, insulin-to-carbohydrate ratios, the amount of carbohydrate to be consumed, and the amount of currently active insulin), different options for bolus delivery, bolus history and other memory functions, download to a personal computer, upload to a web-based server, and possibility of concomitant continuous glucose monitoring.[5,6]

Indications

Three main insulin pump manufacturers, including Animas Canada, Disetronic Medical Systems, and Medtronic of Canada, were contacted for information about indications and contraindications for using insulin pumps.

According to information provided by two manufacturers (Medtronic of Canada and Disetronic Medical System), generally an insulin pump "is indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus for persons requiring insulin."

Medtronic of Canada suggests that appropriate candidates for an insulin pump represent those patients who demonstrate:

- the ability to self-monitor blood glucose levels frequently,
- the motivation to achieve and maintain improved blood glucose control,
- compliance with dietary and insulin regimen consistent with the use of an insulin pump,
- realistic expectations of an insulin pump to manage their diabetes, and
- reliability to maintain regular appointments with their healthcare providers.

Contraindications

According to Medtronic of Canada, IPT is not recommended for patients who are unwilling or unable to perform a minimum of four blood glucose tests per day and to maintain contact with their healthcare professional. Furthermore, successful operation of an insulin pump requires good vision and hearing. Although features exist to help facilitate pump usage, Medtronic of Canada does not recommend the use of this product by patients whose impaired vision or hearing does not allow for full recognition of the pump's signals and alarms.

According to Disetronic Medical Systems, there are no explicit contraindications for the ACCU-CHEK Spirit insulin pump itself; however, there are specific situations and patient conditions where use of the pump is inappropriate; for example, patients with a cardiac pacemaker or deliberate contact with water. These limitations are generally not unique to the ACCU-CHEK Spirit pump but are cautions that any patient using an insulin pump should abide by.

Some authors have suggested that contraindications to IPT extend beyond poor compliance and unwillingness or inability to calculate meal doses or to carry out at least four blood glucose tests daily. They suggest contraindications also include evidence of psychiatric conditions like severe recurrent or unresolved depression, history of suicide attempts, and severe eating disorders.[5] It was reported that, however, if the caring team is especially dedicated, patients in these categories could

also benefit from IPT.[5] Blindness and deafness are not absolute contraindications for IPT. The available evidence indicates that untoward events during IPT happen mainly in poorly selected patients or when the caring team is insufficiently staffed, not well coordinated, or inadequately trained in pump use.[5]

Types of insulins

Insulins used during IPT have evolved from animal-derived insulin to human insulins obtained by recombinant DNA technology and to insulin analogues.[5] Insulin preparations are primarily produced by recombinant DNA technology and are formulated either as structurally identical to human insulin or as a modification of human insulin (insulin analogues).[7]

The first long-acting preparation, protamine zinc insulin, was introduced in the 1930s and was used once daily without additional short-acting regular insulin.[8] In the 1950s intermediate-acting neutral protamine Hagedorn (NPH) and insulin zinc (lente) were introduced, used as a twice daily "split-mix" regimen of NPH and regular insulin.[8] By the early 1980s purified pork insulin and then recombinant human insulin that eliminate insulin allergy and immune-mediated lipoatrophy became available.[8] Conventional insulins include regular insulin and NPH insulin, which are less effective in mimicking the normal pattern of basal and postprandial endogenous secretion of insulin.[9]

During the 1990s reports from the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study led to a renewed interest in developing safer insulin formulations that more closely duplicate the basal and mealtime components of endogenous insulin secretion. This interest has yielded insulin analogues that are characterized by action profiles that afford more flexible treatment regimens with a lower risk of the development of hypoglycemia.

Rapid-acting insulin lispro was the first developed insulin analogue, followed by insulin aspart. Insulin lispro and aspart exhibit important pharmacokinetic and pharmacodynamic advantages over regular insulin, including significantly faster absorption, earlier onset, and shorter duration of action.[10] Long-acting insulin analogues include glargine and detemir (Table T.2).

Table T.2: Types of insulins (trade name)[a]

Rapid-acting analogues (onset 10 to 15 minutes, up to 3 to 5 hours)
• Insulin lispro (Humalog)
• Insulin aspart (NovoRapid)
• Insulin glulisine (Apidra)
Short-acting insulins (onset 30 minutes, 6.5 hours)
• Humulin-R
• Novolin ge Toronto
Intermediate-acting insulins (onset 1 to 3 hours, up to 18 hours)
• Humulin-N
• Novolin ge NPH
Long-acting basal insulin analogues (onset 90 minutes, up to 24 hours)
• Insulin detemir (Levemir)
• Insulin glargine (Lantus)

[a]Source: Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada[7]

Basal-bolus insulin delivery

From a clinical perspective, insulin replacement therapy consists of basal insulin, prandial (bolus) insulin, and a correction dose supplement.[8] Regular and NPH insulin span both the prandial and basal components of insulin replacement, whereas insulin analogues target each of these components separately.[8]

The insulin pump is an open-loop system able to simulate the pattern of insulin secretion with a continuous 24-hour "basal" delivery of insulin upon which are superimposed meal-time boluses.[3] Insulin pumps are programmed to deliver insulin as a basal dose, which is pumped slowly throughout the day and night, and as additional bolus doses to control glucose levels around mealtimes or to correct high blood glucose levels.[3] Rapid- or short-acting insulin is used in the pump for both bolus and basal delivery.[11]

The basal rate is set to the minimum insulin needed to suppress gluconeogensis and ketogenesis while keeping blood glucose levels within the normal range without inducing hypoglycemia. The meal-time boluses are calculated with the use of an algorithm and depend on the caloric and nutritive composition of the meal, the capillary glucose concentration before the meal, and the anticipated level of physical activity after the meal.[2]

The basal and bolus functions of the insulin pump permit separate determinations and adjustments of both these insulin requirements as well as flexibility in timing, amounts of nutritional intake, and physical activity, allowing for wide variations in lifestyle.[2] Some pumps offer a bolus calculator function to facilitate mealtime bolus calculations based on several parameters relating both to the patient and the food being consumed.[3]

Calculation of total daily insulin requirements at the time of pump treatment initiation depends on the insulin requirement while on MDI and the level of glycemic control. In children with good glycemic control and a low frequency of hypoglycemia, the total dose may need to be reduced by 10% to 20%, and with frequent hypoglycemia the dose should be reduced by 20%.[2] Typically 30% to 50% of the total daily dose is required for basal needs, and this is programmed in hourly intervals according to the circadian variation of the patient's insulin sensitivity, which is age dependent.[2]

Blood glucose monitoring

Patients with T1DM using insulin pumps typically perform a minimum of 4 to 6 daily measurements of blood glucose by using stand-alone finger-stick blood glucose meters.[3] Some insulin pumps offer wireless connection to blood glucose meters. Blood glucose reassign results may be transmitted to the pump or entered into the pump by the user, allowing the patient to adjust therapy accordingly.[3]

Compared to conventional blood glucose monitoring, continuous glucose monitoring (CGM) can provide greater details about the direction, magnitude, duration, and frequency of glucose level fluctuations and possible causes of glucose fluctuation in response to meals.[6] Recently introduced real-time CGM systems allow users to see glucose values every 1 to 5 minutes, providing an opportunity for much closer monitoring and for more rapid adjustments to reduce glucose variability and to avoid hypo- or hyperglycemia.[6] Most CGM systems also provide additional features to minimize glucose variability, including graphics to indicate glucose trends and alarms to signal values that are outside of a pre-specified target range.[6]

Potential benefit of IPT over MDI

MDI consisting of three or more daily insulin injections remain the most common method of delivering intensive insulin therapy. MDI therapy has been revolutionized by the introduction of

both long- and rapid-acting insulin analogues. A basal-bolus approach that combines long-acting insulin glargine or insulin detemir with pre-meal injections of rapid insulin analogues has emerged as the "gold standard" for intensive MDI therapy in adult patients with T1DM.[12] For bolus doses before meals, rapid-acting insulins such as aspart, lispro, or glulisine are the preferred choices because of their rapid onset and relatively short duration of activity. Rapid-acting insulins reach peak concentrations twice as high as and within half the time of regular insulin.[1] For basal insulin requirements, intermediate-acting (e.g., NPH) or long-acting (e.g., glargine, determir) insulins can be used. MDI therapy based on long-acting insulin analogues is more efficacious than MDI therapy based on older types of insulins, such as NPH or isophane. Therefore, analogue-based MDI therapy should be used as the comparator for IPT therapy in patients with T1DM.[13]

With MDI a syringe or pen is used to deliver insulin. The available pen devices range from disposable pens, which are supplied to the patient prefilled from the pharmacy, used until empty, and then discarded, to refillable digital pens, some of which have the ability to "remember" prior insulin doses.[14] Disposal pens are generally easy to use after a short training session. Refillable pens are slightly more complex to operate but have more advanced features (such as dose memory) and cause less environmental waste than the disposal pens.[14]

One major potential benefit of IPT over MDI is a reduction of glycemic variability through tighter, more precise glycemic control, which decreases the risk for micro- and macrovascular complications.[1] However, this has not yet been confirmed by primary research evidence (communication with Expert Advisory Group, December 2009). Another important potential benefit of IPT over MDI is reduced severe hypoglycemic events. Intensive insulin therapy is associated with a higher risk for hypoglycemia compared with conventional therapy. Theoretically IPT should decrease the incidence of severe hypoglycemia because it delivers small doses of subcutaneous insulin throughout the day that can be adjusted based on patient-specific requirements.[1]

IPT is the closest to the physiologic method of insulin delivery currently available and offers the possibility of more flexibility and more precise insulin delivery than MDI.[15] With IPT, insulin administration is likely to be more precise and better matched to food intake and there is less variability of insulin absorption.[2] This is particularly important for young children because recurrent episodes of hypoglycemia at a young age have been associated with neuro-cognitive dysfunction.[2]

Health Canada and US FDA approval

Insulin pumps and insulins that have been approved by Health Canada and US Food and Drug Administration (FDA) are listed in Tables T.3 to T.5.

Table T.3: Insulin pumps approved by Health Canada[a]

Manufacturer	Device name	Licence no.	First issue date
Animas Corporation	R-1000 Series Insulin Pump	27789	2001-03-02
	IR 1000 Insulin Infusion Pump	60054	2002-07-11
	IR 122 Insulin Pump (various colours)	65727	2004-08-31
	Animas 2020 Insulin Infusion Pump (various colours)	65727	2007-06021
	Animas 2020 Insulin Infusion Pump (warranty replacement, various colours)	65727	2007-06021
	OneTouch Ping Insulin Infusion Pump (warranty replacement)	80217	2009-07-14

Disetronic Medical Systems AG	D-Tronplus-Insulin Infusion Pump	61348	2003-01-02
	ACCU-CHEK Spirit Insulin Pump	68823	2005-07-12
	Disetronic H-Tron Plus Insulin Infusion Pump	11524	2008-04021
Medtronic MiniMed	MiniMed 506 Insulin Pump	13790	1999-11-01
	MiniMed 507 Insulin Pump	13791	1999-11-01
	MiniMed 507C Insulin Pump	12315	1999-09-21
	MiniMed 508 Insulin Pump	14968	1999-12-02
	Paradigm Insulin Infusion Pump	38347	2002-05-17
	Paradigm 722 Insulin Infusion Pump	62859	2005-10-12
	Paradigm 522 Insulin Pump	62859	2005-10-12
Smiths Medical MD Inc.	Deltec Cozmo 1700 Insulin Infusion Pump	62735	2003-07-21

[a]Source: Health Canada. Medical Devices Active Licence Listing. www.mdall.ca (accessed 29 July 2009[16]

In March 2009, Smiths Medical MD Inc. announced their intent to stop selling Deltec Cozmo Insulin Pumps and manage an orderly, carefully controlled exit from the diabetes business over time.[17]

Table T.4: Insulin pumps approved by the US Food and Drug Administration[a]

Company	Device name
Abbott Diabetes Care Inc.	Aviator Insulin Pump
Animas Corporation	Model R1000 IR Insulin Infusion Pump
	Model IR 1200 Insulin Pump
	R1000 Series Insulin Pump
BD Becton Dickinson Vacutainer Systems Preanalytic	Becton Dickinson 1000 Insulin Pump
Cardiac Pacemakers Inc.	Betatron I Ambulatory Insulin Pump
Delta Medical Industries	Acu-Rynge Insulin Pump #SP-250
Disetronic Medical Systems AG	ACCU-CHEK Insulin Pump Configuration Software (standard) Model 04625137001; ACCU-CHEK Insulin Pump Configuration Software
Medix Medical Electronics (USA) Inc.	Insulin Pump Insumat 229
Medtronic MiniMed	Modification to Medtronic MiniMed Paradigm Model 512 Insulin Pump
	MiniMed Model 506 External Insulin Pump
	Medtronic MiniMed Paradigm Insulin Pump Models MMT-515 and MMT-715
	Medtronic MiniMed Paradigm Insulin Pump Model MMT-712E
	Modified MiniMed MDL404-SP/504-S Drug Insulin Pump
	MiniMed Insulin Pump Model 505
	MiniMed 508 Insulin Pump
	Medtronic MiniMed Paradigm Model 511 Insulin Pump
MiniMed Inc.	Medtronic MiniMed Paradigm Insulin Pump Model MMT-712
	MiniMed Paradigm Insulin Pump Model 511
	Medtronic MiniMed Paradigm Model 512 Insulin Pump and the BD Paradigm Link Glucose Meter
Nipro Diabetes Systems Inc.	Amigo Insulin Pump
Sooil Development Co. Ltd.	Dana Diabecare II Insulin Pump & Superline-Easyrelease Soft-Release-ST & Soft-Release-R Infusion Sets

[a]Source: US FDA. 510 (K) Premarket Notification (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm)

Table T.5: Insulin and insulin analogues approved by Health Canada[a]

Product name	Company	Number of active ingredients	Class	Product monograph
Apidra (10 mL vial)	Sanofi-Aventis Canada Inc.	1	Human	Yes
Apidra (3 mL Cartridge)	Sanofi-Aventis Canada Inc.	1	Human	Yes
Apidra (3 mL Solostar Disposable Prefilled Pen)	Sanofi-Aventis Canada Inc.	1	Human	Yes
Humalog	Eli Lilly Canada Inc.	1	Human	Yes
Humalog (Cartridge/Kwikpen)	Eli Lilly Canada Inc.	1	Human	Yes
Humalog MIX 25 (Cartridge/Kwikpen)	Eli Lilly Canada Inc.	2	Human	Yes
Humalog MIX 25 (Pen)	Eli Lilly Canada Inc.	2	Human	Yes
Humalog MIX 50 (Cartridge/Kwikpen)	Eli Lilly Canada Inc.	2	Human	Yes
Humalog Pen	Eli Lilly Canada Inc.	1	Human	Yes
Humulin 30/70 (Insulin Human Biosynth Inj)	Eli Lilly Canada Inc.	2	Human	Yes
Humulin 30/70 Cartridge	Eli Lilly Canada Inc.	2	Human	Yes
Humulin N Cartridge	Eli Lilly Canada Inc.	1	Human	Yes
Humulin N Inj 100 Unit/mL	Eli Lilly Canada Inc.	1	Human	Yes
Humulin N Pen	Eli Lilly Canada Inc.	1	Human	Yes
Humulin R Cartridge	Eli Lilly Canada Inc.	1	Human	Yes
Humulin R Inj	Eli Lilly Canada Inc.	1	Human	Yes
Hypurin NPH Insulin Isophane Pork	Wockhardt UK Ltd.	1	Human	Yes
Hypurin Regular Insulin Pork	Wockhardt UK Ltd.	1	Human	Yes
Insulinum	Standard Homeopathic Canada Inc.	1	Human	Yes
Lantus (3 mL Solostar prefilled disposable pen)	Sanofi-Aventis Canada Inc.	1	Human	Yes
Lantus (cartridge)	Sanofi-Aventis Canada Inc.	1	Human	Yes
Lantus (vial)	Sanofi-Aventis Canada Inc.	1	Human	Yes
Levemir Penfill	Novo Nordisk Canada Inc.	1	Human	Yes
Novolin GE 30/70 Inj Sus	Novo Nordisk A/S	2	Human	Yes
Novolin GE 30/70 Penfill Inj Sus	Novo Nordisk A/S	2	Human	Yes
Novolin GE 40/60 Penfill Inj Sus	Novo Nordisk A/S	2	Human	Yes
Novolin GE 50/50 Penfill Sus Inj	Novo Nordisk A/S	2	Human	Yes
Novolin GE NPH Inj Sus 100 U/mL	Novo Nordisk A/S	1	Human	Yes
Novolin GE NPH Penfill Inj Sus 100 U/mL	Novo Nordisk A/S	1	Human	Yes
Novolin GE Toronto Inj 100 U/mL	Novo Nordisk A/S	1	Human	Yes
Novolin GE Toronto Penfill Inj Liq 100 U/mL	Novo Nordisk A/S	1	Human	Yes
Novomix 30 (Penfill Cartridge)	Novo Nordisk Canada Inc.	2	Human	Yes
Novorapid	Novo Nordisk Canada Inc.	1	Human	Yes
Novorapid (10 mL vial)	Novo Nordisk Canada Inc.	1	Human	No

[a]Source: Health Canada Drug Product Database 2009.[18] All of the listed insulins have an "active" status.

Diffusion of technology

Three insulin pump manufacturers, including Animas Canada, Disetronic Medical System, and Medtronic of Canada, were contacted for information regarding the diffusion of their insulin pumps in Canada and Alberta.

Canada

Animas Canada has been operating in Canada as a division of LifeScan Canada Ltd. (a Johnson & Johnson company) since the fall of 2006. Prior to 2006 Animas insulin pumps and related supplies were made available to patients via a privately owned distributor.

Disetronic Medical System began supplying insulin pumps into Canada in 1993. In 2006 Disetronic launched the ACCU-CHEK Spirit insulin pump system in Canada.

Insulin pumps have been available in Canada since 1983 from the company MiniMed, which was represented in Canada by a distributer until 2001. Medtronic Inc. purchased MiniMed worldwide in 2001 and has been responsible for regulatory requirements, sales, and distribution in Canada since 2002.

With respect to numbers of pump users, according to the feedback from the three manufacturers, no Canadian pump registry is currently in place.

Animas Canada estimated that less than 50% of patients with T1DM currently use insulin pumps. The estimates of the total number of insulin pump users in Canada range from 11,000 (estimated by the Disetronic Medical System) to 16,000 to 18,000 patients (estimated by Medtronic of Canada). No information is available regarding the distribution of pump users in T1DM and T2DM.

In Ontario, about 1700 children and youth are currently treated with IPT with financial support from the Ministry of Health and Long-Term Care.[19]

Alberta

Estimates of the total number of insulin pump users in Alberta also vary, ranging from 700 (estimated by Disetronic Medical System Inc) to between 700 and 950 patients (estimated by Medtronic of Canada). No information is available regarding the distribution of pump users in different types of diabetes.

International

Approximately 1% of patients with T1DM in the United Kingdom and Denmark use insulin pumps,[20] compared to 10% to 15% in Germany and the Netherlands, and 20% in the United States and Israel.[3,20] An increase in the use of IPT in pediatric patients has been observed in some European countries. In Sweden, the usage of IPT in the pediatric population with diabetes was 7.5% in 1999 and is now approaching 20%.[21,22] The cost of pumps and pump accessories has been reimbursed since 1997.[21] In Germany and Austria there has been a major increase in IPT as the first line treatment at the time of diagnosis of T1DM, especially in very young children.[23]

Safety issues

Early devices suffered reliability problems and lacked some safety features. There were also reports of increased incidences of diabetic ketoacidosis, severe hypoglycemia, and subcutaneous skin infections among pump users.[3,24] However, patient selection criteria and limited patient education, rather than failings of the pumps themselves, may have contributed significantly to the incidences of adverse events and complications.[3]

Diabetic ketoacidosis

This is the second most frequently reported acute complication associated with the use of insulin pumps.[25] Diabetic ketoacidosis during IPT is rapid in onset, and pump users have to be instructed to react promptly to technical problems or unexplained hyperglycemia. Early studies reported a high rate of diabetic ketoacidosis during IPT, but the frequency of this serious complication decreased during the 1990s, presumably because of increased patient and physician experience and technical improvements.[5] An education program about diabetic ketoacidosis risk prevention should be provided.[25]

Severe hypoglycemia

The Diabetes Control and Complications Trial (DCCT)[26] and the Danish-British multicentre survey[27] indicate that severe hypoglycemia affects about one-third of patients with established T1DM but that only 5% of these patients account for half of all episodes. Severe hypoglycemia remains one of the most feared complications, and risk factors may include age, duration of diabetes, tight glycemic control, or altered hypoglycemic awareness.[28] Tight glycemic control in the DCCT attained by MDI or IPT was associated with a 3-fold increase in severe hypoglycemia.[29]

IPT is thought to decrease hypoglycemic events by increasing hypoglycemia awareness, improving counterregulatory responses, decreasing insulin requirements, and allowing a more precise tuning of blood glucose levels (by keeping slightly higher glucose levels in patients prone to hypoglycemia).[5] Recurrent severe hypoglycemia and hypoglycemia unawareness in patients on MDI regimen was a major indication for starting IPT.[5,30]

The threat of pump malfunction that leads to excessive insulin delivery was an early concern after the introduction of IPT; this is, however, not an issue with the current generation of pumps, which are equipped with numerous safety features.[15]

Infection and inflammation of the infusion site

Skin infection or inflammation at the infusion site is the most frequently reported complication of IPT and a major reason for discontinuation of this treatment.[25] Moreover, this complication can be serious because an infected infusion site has been implicated in the development of toxic shock syndrome and bacterial endocarditis; the latter can lead to death.[25]

Pump malfunction

Various pump malfunctions have been reported, including pump breakdown, battery or drive mechanism failure, corrosion of battery or other components, memory loss, inability to start pumping out of an electrical "lock" position, and alarm malfunctions.[25] Various types of infusion set obstruction, leakage from the infusion site while the needle is placed in the subcutaneous tissue or if the cannula is dislodged, leakage at the infusion set connection (between the syringe and the infusion tubing), or leakage at the infusion tubing (between the syringe connection and the injection site) have been reported.[25] The pump alarm system does not usually detect leakage. Moreover, in more than 85% of reported occlusion events, the metabolic deterioration occurs before the activation of high-pressure alarms.[25] Failure of infusion sets is often associated with transient loss of metabolic control and is a major cause of diabetic ketoacidosis.[25] Most pump malfunctions were reported in the late 1980s; however, pump malfunction remains frequent even today despite great advances in IPT technology.[5]

Methodology

Literature search

A comprehensive literature search was conducted to identify the most recent systematic reviews and health technology assessments (HTAs) of randomized controlled trials (RCTs) or newly published RCTs that compared IPT with MDI. A detailed description of the literature search strategy, including sources (databases, websites, grey literature), dates searched, and search terms used, is provided in Appendix T.A.

Search for systematic reviews/HTAs

A literature search was conducted using key health information resources, including MEDLINE, EMBASE, Cochrane Library, and the Centre for Reviews and Dissemination (CRD) databases to identify systematic reviews/HTAs of RCTs published between January 2004 and June 2009. The search was limited to the past 5 years because of the ongoing evolution in insulin preparations and insulin pumps, with new generations of insulin pumps coming to the market every 5 years.

Search for new RCTs

MEDLINE, EMBASE, and CENTRAL were searched for RCTs published since 2006. Because the last search dates were March 2008 in the best quality systematic review (which did not include pregnant women),[31] and November 2006 in the most recent systematic review[32] on pregnant women, we used the year 2006 as the starting date for searching for new RCTs. Web of Science, Biosis Previews, and CINAHL were searched from 1999 onward because searches in these databases were not conducted in the other systematic reviews.

Search for grey literature

Grey literature was searched for local context and regulatory status (Health Canada and US FDA). A thorough review of HTA agency websites was conducted, as were searches for clinical practice guidelines and ongoing clinical trials.

Reference lists from the included studies were also checked for other relevant studies.

Selection of literature

Titles and abstracts from the literature search were screened by one HTA researcher (BG) and one information specialist (TC), and full-text publications of relevant articles were retrieved. Eligibility of key studies (i.e., systematic reviews/HTAs of RCTs and new RCTs) was determined by two researchers (BG and PC) according to the predefined inclusion and exclusion criteria (Appendix T.A: Methodology/study selection). Excluded studies are listed in Appendix T.B.

Quality assessment

The methodological quality of the included studies was appraised by two independent researchers (BG and PC). The quality of the selected systematic reviews and HTAs was appraised using a previously developed in-house tool (Appendix T.C). The quality of the new RCTs was appraised using the Cochrane risk of bias tool[33] (Appendix T.C), as suggested by the corresponding author of the best quality systematic review.[31] The quality results from the two researchers were compared, and discrepancies between the researchers were resolved by discussion.

Data extraction

Information on the safety and efficacy or effectiveness of IPT compared to MDI in patients with T1DM was extracted from each included study according to predeveloped data extraction forms (see Appendix A: Methodology/Data extraction).

Data synthesis

A qualitative synthesis was performed for research findings from the included systematic reviews, HTAs, and new RCTs.

Description of the included studies

Characteristics of the included studies

The literature search identified 609 citations using the search strategy described in Appendix T.A. On closer examination of the full text articles that appeared to be potentially relevant, eight systematic reviews[31,32,34-39] (Table T.6), two HTAs,[40,41] and six new RCTs[6,22,28,42-44] (Table T.7) that met the inclusion criteria were selected for analyses and synthesis. Excluded systematic reviews and RCTs and the reasons for exclusion are listed in Appendix T.B.

Data extracted from the included systematic reviews and HTAs regarding study objective, search strategy, selection criteria, study characteristics, outcomes, and conclusions are presented in Appendix T.D (Tables T.D.1 and T.D.2). Table T.D.3 contains information regarding insulin delivery systems and types of insulins used in the studies included in the systematic reviews.

Details extracted from the new RCTs regarding study objective, study design, patient characteristics, intervention and comparator, and outcomes are presented in Table T.D.4. Table T.D.5 contains a summary of information specific to the insulin delivery systems and type of insulins used in the RCTs. Information obtained from new RCTs regarding training or education and equipment required for IPT is summarized in Table T.D.6.

As shown in Table T.6, of the eight systematic reviews, four[31,34-36] targeted the general population (including adults and children), one[37] focused on preschool children, one[38] on children and adolescents, and two[32,39] on pregnant women. Seven of the eight reviews performed meta-analyses for some outcomes where appropriate.

Some reviews included both RCTs and nonrandomized trials (e.g., before-after comparative studies), and some reviews also included studies that targeted patients with T2DM but reported results separately for T1DM or T2DM. Only information obtained from RCTs that compared IPT with MDI in patients with T1DM was extracted and presented in this report.

In the two reviews[32,39] on pregnant women the researchers attempted to examine the safety and efficacy of IPT in all pregnant women with diabetes. They included six RCTs in total; five targeted T1DM only, whereas one included patients with T1DM and T2DM but reported results separately for the two patient groups. Therefore, these two reviews were considered to meet our criteria.

The review by Fatourechi and colleagues[31] included only 13 RCTs on patients with T1DM that were published between 2002 and March 2008. The reason for this date restriction was the rapid evolution of insulin pumps and insulin types. Other reviews included older RCTs, which may have impacted their final results and not reflect the actual effect of the newer technologies.

Of the two HTAs identified, the one prepared by the Medical Advisory Secretariat, Ontario Ministry of Health and Long-term Care,[40] included seven systematic reviews or meta-analyses and five RCTs

(one was a conference abstract) published between January 2000 and March 2009 involving adult patients with T1DM. No meta-analysis on the RCTs was performed for any outcomes due to missing data or differences in reporting results.

The HTA prepared by the New Zealand Health Services Assessment Collaboration[41] was an update of an NHS HTA report[45] and included one systematic review and six RCTs (two for adults and four for children and adolescents) for T1DM as well as a systematic review for pregnant women with diabetes.[32]

Both HTAs assessed safety, effectiveness, and economic implications of IPT compared with MDI in patients with T1DM and T2DM, and reported results for T1DM and T2DM separately. For the purpose of this report, only data on the safety and efficacy or effectiveness results obtained from patients with T1DM were extracted. These are presented in Appendix D (Table T.D.2).

Table T.6: Overview of the included systematic reviews

Study	Target population	Literature search	No. of RCTs on T1DM	Length of follow-up (month)
Fatourechi et al. 2009[31]	Adults, preschool children, children and adolescents Pregnancy was excluded.	MEDLINE, EMBASE, Cochrane's CENTRAL 2002 to March 2008	13	1.2 to 12.1
Monami et al. 2009[34]	Adults, preschool children, children and adolescents	MEDLINE Up to 10 July 2008	11	3.7 to 12.1
Pickup & Sutton 2008[35]	Adults and children and adolescents Pregnant women were excluded.	MEDLINE, EMBASE 1996 to 2006	6	1.25 to 7
Jeitler et al. 2008[36]	Adults, preschool children, children and adolescents Pregnant women were excluded.	MEDLINE, EMBASE, CENTRAL Cochrane Database of Systematic Reviews, DARE, HTA Database, National Health Service Economic Evaluation Database for secondary literature Last update 5 March 2007	20	1.2 to 24
Churchill et al. 2009[37]	Preschool children (≤ 6 years)	MEDLINE, CINAHL 1996 to March 2008	3	6 to 12
Pankowska et al. 2009[38]	Preschool children, children and adolescents	MEDLINE, EMBASE, Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register) Up to October 2007	6	4 to 12
Farrar et al. 2007[32]	Pregnant women	Cochrane Pregnancy and Childbirth Group's Trials Register* November 2006	2	Until delivery
Mukhopadhyay et al. 2007[39]	Pregnant women	MEDLINE (1974 to April 2006), CENTRAL, CINAHL, EMBASE (1974 to April 2006)	6	Until delivery

* Search methods involved 1) quarterly searches of CENTRAL, 2) monthly searches of MEDLINE, 3) hand searches of 30 journals and the proceedings of major conferences, and 4) weekly current awareness searches of a further 37 journals

Abbreviations: HTA: health technology assessment; no.: number; RCTs: randomized controlled trials; T1DM: type 1 diabetes

As shown in Table T.7, of the six new RCTs comparing IPT with MDI, three targeted the adult population and the other three focused on children and adolescents. No new RCTs on pregnant women were found. The total number of study participants ranged from 21 to 72, with a follow-up period ranging from 3.5 months to 2 years.

Table T.7: Overview of the included new randomized controlled trials

Study	Target population	Number of participants	Follow-up (months)
Bolli et al. 2009[42]	Adults	50	5.6
Peyrot & Rubin 2009[6]	Adults	28	3.7
Thomas et al. 2007[28]	Adults	21	5.6
Nabhan et al. 2009[43]	Preschool children (< 5 years)	42	12
Nuboer et al. 2008[44]	Children and adolescents (4 to 16 years)	38	3.5
Skogsberg et al. 2008[22]	Children and adolescents (7 to 17 years)	72	24

There was a great deal of overlap in the RCTs included in the eight systematic reviews; the total number of RCTs (from both systematic reviews and new RCTs) for each patient group is presented in Table T.8. A small number of RCTs on adult patients were published in the past 5 years (i.e., 2004 onward), and no RCTs on pregnant women have been conducted within the past 5 years.

Table T.8: Number of the included randomized controlled trials (RCTs)

Patient group	No. of RCTs included in SRs (No. of RCTs published since 2004)	No. of new RCTs	Total No. of RCTs (No. of RCTs published since 2004)
Adults (≥ 19 years)	21 (4)	3	24 (7)
Preschool children (0 to 6 years)	4 (4)	1	5 (5)
Children and Adolescents (7 to 18 years)	5 (1)	2	7 (3)
Pregnant women	6 (0)	0	6 (0)

Abbreviations: no.: number; RCTs: randomized controlled trials; SRs: systematic reviews

Quality of the included studies

Level of available evidence

According to the criteria developed by the UK Centre for Evidence Based Medicine,[46] the level of evidence for the included systematic reviews of RCTs is considered as level 1a, and the level of evidence for the included individual RCTs is considered as level 1b; these two types of studies represent the highest levels of evidence for the efficacy of IPT compared with MDI for the treatment of T1DM.

Quality of the systematic reviews and health technology assessments

Quality assessment results for each of the eight systematic reviews and two HTAs are presented in Appendix T.C (Table T.C.1 and Table T.C.2).

The methodological quality of five of the systematic reviews was rated as "average," and one was rated as "poor";[34] only two reviews[31,38] received a good-quality rating. Most reviews searched databases beyond that of MEDLINE, and data were extracted by two independent reviewers. All seven meta-analyses reported precision of results and tested for heterogeneity. Conclusions from all of the eight reviews were supported by the results presented. However, only one review[31] used and reported a standardized method for data extraction. In three reviews[34-36] it was not clear whether quality assessment was performed by two independent reviewers.

The review by Fatourechi and colleagues[31] met all six key criteria and was considered the best quality review. The reviewers also contacted authors of all included primary studies to verify the data extracted from their studies and requested data not available in the published record. Responses were received from the authors of almost all of the primary studies. This review included both adults and children but excluded pregnant women. The present report builds on this review for the adult and children populations.

Both HTAs[40,41] met Cook's criteria[47] for systematic reviews. Therefore, the same quality assessment tool for systematic reviews was used for the two HTAs. The major limitation of these two HTAs is related to the number of reviewers for data extraction and quality assessment; one HTA[40] did not provide this information, and in the other[41] only one reviewer performed data extraction and quality assessment.

Quality of the new RCTs

Quality assessment results for each of the six new RCTs are presented in Appendix T.C (Table T.C.3).

Using the Cochrane risk of bias tool, five of the six RCTs appeared to be free of suggestion of selective outcome reporting. However, none of the studies reported on the methods for sequence generation. Blinding of the type of intervention from clinicians and participants was not possible because of the nature of the treatment. Although assessment of outcomes could be blinded, this was not elucidated in any of the studies. Allocation concealment was reported in only two RCTs.[42,44] Four of the six RCTs[6,22,43,44] could not eliminate other problems that have the potential for risk of bias.

Overall, there was a lack of reporting of the information required to assess the six aspects included in the risk of bias tool. Thus, "unclear" ratings were given for more than half of the items. The authors of these RCTs were not contacted for more details because of time constraints. An evaluation based on the published, reported data, indicated that none of the six RCTs were judged to have "low" risk of bias; all studies were judged to have "unclear" to "high" risk of bias.

Evidence on safety

Severe hypoglycemia

Severe hypoglycemia is one of the main safety outcomes assessed in all of the included systematic reviews. Of the four systematic reviews that included adults and children, only one[36] reported this outcome separately for different age groups; however, most of the RCTs on adults included in this review are old.

The best quality review by Fatourechi et al.[31] included 13 RCTs on T1DM that enrolled patients with poor glycemic control or at low risk of hypoglycemia. A meta-analysis of this outcome indicated no significant differences in the rate of severe hypoglycemia episodes between patients in the IPT and MDI groups, with the point estimate favouring IPT. Use of insulin analogues in the MDI group did not significantly alter the hypoglycemia outcome. There was no correlation between the end-of-study A1C levels achieved and the treatment effects.

Because no age-specific subgroup analysis was performed for this outcome, raw data on severe hypoglycemia from each of the studies included in this review for different age groups are presented in Table T.9; percentages of patients with at least one severe hypoglycemia episode were calculated and are presented in the brackets.

Table T.9: Frequency of severe hypoglycemia

RCTs included in the best quality review[31]	No. of patients with ≥ 1 SH episodes/no. of patients allocated to IPT (calculated %)	No. of patients with ≥ 1 SH episodes/no. of patients allocated to MDI (calculated %)
Adults (five RCTs)		
Brutommesso 2008	4/39 (**10.3**)	2/39 (**5.1**)
Hirsch 2005	2/99 (**2.0**)	3/99 (**3.0**)
Hoogma 2006	11/229 (**4.8**)	22/229 (**9.6**)
Lepore 2003	2/16 (**12.5**)	3/16 (**18.8**)
Thomas 2007	2/7 (**28.6**)	2/7 (**28.6**)
Preschool children (four RCTs)		
DiMeglio 2004 (1.8 to 4.7 yr)	1/20 (**5**)	1/17 (**5.9**)
Fox 2005 (1 to 6 yr)	0/11 (**0**)	2/11 (**18.2**)
Opiari-Arrigan 2007 (3.1 to 5.3 yr)	0/8 (**0**)	2/8 (**25**)
Wilson 2005 (1.7 to 6.1 yr)	1/9 (**11.1**)	1/10 (**10**)
Children and adolescents (four RCT's)		
Cohen 2003 (14 to 18 yr)	1/15 (**6.7**)	1-4/13 (**7.7-30.8**)
Doyle 2004 (8 to 21 yr)	0/16 (**0**)	4/15 (**26.7**)
Pozzilli 2003 (8 to 32 yr, mean 18)	NA**	NA**
Weintrob 2003/04 (9 to 14 yr)	1/23 (**4.3**)	3/23 (**13.0**)

*Abbreviations: IPT: insulin pump therapy; MDI: multiple daily injection; NA: not available; no.: total number; RCTs: randomized controlled trials; SH: severe hypoglycemia; yr: year
**Contact of the author of this RCT: approximately 20 SH episodes per year in each group

Results on severe hypoglycemia episodes reported in the six new RCTs are presented in Table T.10, and the potential association of this outcome with the duration of diabetes, history of severe hypoglycemia, types of insulin used in MDI (regular insulin versus long-acting insulin analogues), and length of follow-up are explored.

Table T.10: Severe hypoglycemia episodes reported in six new RCTs

Study	Frequency of SH episodes	Patients	Basal-bolus insulins
Adult patients			
Bolli et al. 2009[42] N = 50	Follow-up: 5.6 months **SH**: 2 in each treatment group (nss)	**Diabetes duration** (mean, yrs): 18.5 in IPT group vs. 20.9 in MDI group **History of SH**: none (exclusion: patients with > two SH episodes in the past 6 months)	**IPT**: insulin lispro **MDI**: insulin glargine/insulin lispro
Peyrot & Rubin 2009[6] N = 28	Follow-up: 3.7 months **SH**: 0 in IPT vs. 3 in MDI	**Diabetes duration** (mean, yrs): 25.6 (all patients) **History of SH**: NA	**IPT**: not clear **MDI**: not clear
Thomas et al. 2007[28] N = 21	Follow-up: 5.6 months **SH**: 3 in IPT vs. 2 in MDI (nss)	**Diabetes duration** (mean, yrs): 25 **History of SH**: all patients (inclusion: patients with ≥ 1 SH episodes in the past 6 months)	**IPT**: insulin lispro **MDI**: insulin glargine/insulin lispro
Preschool children			
Nabhan et al. 2009[43] N = 42	Follow-up: 12 months **SH**: 1 in IPT vs. 1 in MDI (nss)	**Diabetes duration** (mean, yrs): 1.8 in both groups **History of SH**: NA	**IPT**: insulin lispro **MDI**: NPH, lente, or glargine/insulin lispro
Children and adolescents			
Nuboer et al. 2008[44] N = 38	Follow-up: 3.5 months **SH**: 2 in IPT vs. 4 in MDI (mean per patient yr 0.29 in IPT vs. 1.1 in MDI, indicating 3-fold decrease)	**Diabetes duration** (mean, yrs): 5.6 in IPT group vs. 4.7 in MDI group **History of SH**: in 10 of 38 patients (inclusion: a history of repeated symptomatic hypoglycemia)	**IPT**: insulin aspart **MDI**: NPH or insulin glargine/insulin aspart or regular insulin
Skogsberg et al. 2008[22] N = 72	Follow-up: 24 months **SH:** 13 in IPT vs. 12 in MDI (nss)	**Diabetes duration** (mean, yrs): ≤ 3 weeks (newly diagnosed) **History of SH**: none	**IPT**: insulin lispro/insulin lispro **MDI**: insulin glargine/insulin lispro

Abbreviations: IPT: insulin pump therapy; MDI: multiple daily injection; N: total number; NA: not available; NPH: neutral protamine Hagedorn; nss: not statistically significant; RCTs: randomized controlled trials; SH: severe hypoglycemia; yr: year

Adults

Findings from systematic reviews: As shown in Table T.9, of the five RCTs on adult patients (two studies excluded patients with a history of severe hypoglycemia or hypoglycemia unawareness), compared to MDI, percentages of patients in IPT who experienced at least one severe hypoglycemia episode were lower in three RCTs, the same in one RCT, and higher in the other; statistical significance of these differences was not available.

Findings from new RCTs: As shown in Table T.10, of the three new RCTs[6,28,42] for adult patients, two[28,42] found no significant difference in severe hypoglycemia episodes between the two treatment

groups. These two studies were similar in terms of durations of diabetes, lengths of follow-up, and types of insulin used for MDI (long-acting insulin glargine for basal injections and rapid-acting insulin lispro for bolus injections) but differed in that one[42] study excluded patients with a history of severe hypoglycemia, whereas the other [28] included such patients. Another study[6] reported no severe hypoglycemia episodes in patients treated with IPT compared to three episodes in MDI group. This study followed patients for only 3.7 months and did not provide clear information regarding patients' histories of severe hypoglycemia and types of insulin used for MDI; thus, this finding needs to be interpreted with caution.

Preschool children

Findings from systematic reviews: As shown in Table T.9, three of four RCTs reported fewer patients in the IPT groups who experienced at least one severe hypoglycemic episode than the MDI group, whereas there was no significant difference in the other study.

Findings from new RCTs: As shown in Table T.10, the only new RCT[43] did not find any significant difference in severe hypoglycemia episodes between the two treatment groups in this very young patient population.

Children and adolescents

Findings from systematic reviews: As shown in Table T.9, similar to the results for preschool children, three (including one RCT that excluded patients with a history of severe hypoglycemia or hypoglycemia unawareness) of four RCTs reported fewer children and adolescents in IPT groups than in MDI groups experienced at least one severe hypoglycemia episodes, whereas the other study did not report this outcome.

Findings from new RCTs: As shown in Table T.10, one new RCT that included children and adolescents with repeated symptomatic hypoglycemia[44] found a 3-fold decrease in severe hypoglycemia episodes in patients treated with IPT compared to MDI, whereas the other RCT[22] that included newly diagnosed children and adolescents reported no significant difference between the two groups. According to Skogsberg and collegues,[22] a possible reason for the lack of difference might be that the registration of severe hypoglycemia episodes was only recorded in each patient's diary, and although the criteria for severe hypoglycemia were clearly described in the study protocol, this parameter could have been interpreted differently among the patients. Including newly diagnosed patients without a history of severe hypoglycemia and the use of insulin glargine and insulin lispro might also have contributed to the lack of difference in this outcome.

Pregnant women

Of the two systematic reviews[32,39] involving pregnant women, one review[39] of six RCTs found that severe hypoglycemia episodes were more frequent with the IPT, but the difference was not statistically significant. The other review[32] of two RCTs that were already included in the first review[39] found no statistically significant difference in maternal severe hypoglycemia episodes between the two treatment groups.

Diabetic ketoacidosis

Adults

Available evidence indicates that diabetic ketoacidosis appears to be infrequent with IPT (Table T.11). Three of the four systematic reviews did not report the incidence of diabetic ketoacidosis. One[36] reported slightly higher frequency of diabetic ketoacidosis in patients treated with IPT based on two RCTs published since 2004.

Of the three new RCTs, no diabetic ketoacidosis occurred with IPT in the two studies, and the other did not report this outcome.

Preschool children

Diabetes ketoacidosis appears to be infrequent in young children. One review[38] reported two episodes in the IPT group compared with none in the MDI group, but the difference was not statistically significant. The new RCT[43] found no diabetic ketoacidosis episode in either treatment group.

Children and adolescents

Two reviews[36,38] found no statistical significant difference in diabetic ketoacidosis between the IPT and the MDI groups.

One new RCT[22] found no diabetes ketoacidosis episode requiring hospital admission in the two treatment groups. This could be a result of a thorough education program for the patients and their families at the onset of their diabetes and the fact that many patients still had some residual beta cell function.

Pregnant women

Of the two systematic reviews[32,39] on pregnant women, one[39] found that diabetes ketoacidosis was more frequent in the IPT group but the difference was not statistically significant, whereas the other[32] did not report this outcome.

Site infection and pump malfunction

As shown in Table T.11, information regarding infection and pump malfunction was not available in some of the systematic reviews and new RCTs. Although infection was not a common event, insulin pump–related problems occurred in some adults, children and adolescents, and pregnant women.

Summary

Currently available evidence does not indicate a significant decrease in severe hypoglycemia episodes in patients on IPT compared to MDI regardless of the age group and the status of the pregnancy. As pointed out by the authors of the best quality review,[31] there is a paucity of evidence in patients at high risk of hypoglycemia (e.g., patients with recurrent severe hypoglycemia or hypoglycemia unawareness). Of the RCTs included in this review, only one pilot trial focused on patients with hypoglycemia unawareness, whereas the largest trial enrolling patients with long-standing T1DM excluded patients with prior history of severe hypoglycemia.

IPT appeared to be as safe as MDI in terms of diabetes ketoacidosis episodes during the treatments; other complications such as infections and pump malfunctions were reported infrequently in the included studies.

Table T.11: Summary of other safety results*

Population	Diabetic ketoacidosis (DKA)	Site infection	Pump malfunction
Adults	**4 SRs** (22 RCTs): 3 SRs: NA 1 SR: 2 RCTs published since 2004: 1 in IPT vs. 0 in MDI; 4 in IPT vs. 0 in MDI **3 new RCTs**: RCT 1: NA RCT 2: 0 in IPT vs. 1 in MDI RCT 3: none	**4 SRs** (22 RCTs): 3 SRs: NA 1 SR: 3 episode in 1 patient in IPT **3 new RCTs**: RCT 1: 1 in IPT RCT 2: NA RCT 3: none	**4 SRs** (22 RCTs): 3 SRs: NA 1 SR: 4 studies reported pump problems **3 new RCTs:** RCT 1: 3 pumps replaced without mechanical failure; 20 occlusion in 9 patients RCT 2: NA RCT 3: NA
Preschool children	**5 SRs** (4 RCTs) 3 SR: NA 1 SR: no DKA in either group 1 SR: 1 study reported 2 episodes in IPT vs. 0 in MDI (nss) **1 new RCT**: none	**5 SRs** (4 RCTs): NA **1 new RCT:** none	**5 SRs** (4 RCTs): NA **1 new RCT:** NA
Children and adolescents	**5 SRs** (5 RCTs) 3 SRs: NA 1 SR: 1 study reported 1 episode in each group 1 SR: 1 study reported 2 episodes in IPT vs. 0 in MDI (nss) **2 new RCTs** RCT 1: 2 in IPT vs. 4 in MDI RCT 2: none	**5 SRs** (5 RCTs): NA **2 new RCTs:** NA	**5 SRs** (5 RCTs): NA **2 new RCTs** RCT 1: NA RCT 2: technical problem 5 in IPT vs. 1 in MDI
Pregnant women	**2 SRs** (6 RCTs) More frequent in IPT group (nss)	**2 SRs** (6 RCTs) NA	**2 SRs** (6 RCTs) Catheter disconnection 3 in IPT (1 RCT), catheter leakage and occlusion not frequent

* Focused on the results obtained from the RCTs published over the past 5 years except for studies on pregnant women
Abbreviations: DKA: diabetes ketoacidosis; IPT: insulin pump therapy; MDI: multiple daily injections; NA: not available; nss: not statistically significant; RCTs: randomized controlled trial; SRs: systematic reviews

Evidence on efficacy

Glycemic control (A1C level)

Glycemic control was measured by A1C in all of the included studies. Pooled weighted mean differences between IPT and MDI groups were reported in some systematic reviews (Table T.12).

Detailed information extracted from the six new RCTs, such as baseline A1C levels, changes in A1C levels in each of the two treatment groups from baseline, or the magnitude of the differences in changes between IPT and MDI, is tabulated in Appendix T.D (Table T.D.4). Reported differences in the magnitudes of A1C reductions between IPT and MDI and some potentially relevant factors such as baseline A1C levels, a history of severe hypoglycemia episodes, types of insulins used, and the length of follow-up are presented in Table T.13.

Adults

The authors of the best quality review[31] performed a subgroup analysis for adult patients and showed that, compared to MDI, IPT yielded an additional A1C reduction of 0.2%, which is not clinically significant (a reduction of 0.5% to 1.0% in A1C was considered clinical significant based on communication with the Expert Advisory Group, 8 May 2009). No significant association was found between the IPT-MDI difference in A1C reduction and the baseline A1C levels.

This review noted that the included studies varied widely with regard to types of insulins and pumps used (see Table T.D.3) but that most used insulin analogues. In the studies published in the past 5 years, Medtronic MiniMed 508 insulin pump was used most frequently; however, this pump is no longer available on the Canadian market.

The results from the three new RCTs[6,28,42] conducted in adult patients were consistent in that there were no statistically significant differences in A1C reductions between IPT and MDI groups. Despite that one RCT[28] enrolled patients with higher baseline A1C levels (mean 8.5% in IPT and 8.6% in MDI) and a history of severe hypoglycemia in the past 6 months, the results from this study was similar to the other study[42] in which patients had lower baseline A1C (mean 7.7% in IPT and 7.8% in MDI) but without previous severe hypoglycemia. As both studies used long-acting insulin glargine for basal injections in MDI, results from these two studies also suggested the nonsuperiority of IPT over glargine-based MDI in terms of A1C reduction in adult patients with T1DM.

Preschool children

The only review[37] that focused on preschool children did not include a meta-analysis for A1C. This review based on three RCTs found no statistically significant differences in A1C changes between the treatment groups at the end of the studies.

Two reviews[31,38] included meta-analyses for this outcome in children (including preschool children, children, and adolescents, no subgroup analysis performed for preschool children only or children and adolescents only) and found that, compared to MDI, IPT reduced A1C by 0.2% to 0.24%; although statistically significant, these reductions are not considered clinically significant.

One new RCT[43] demonstrated significant changes in A1C over time in both groups from baseline but did not find any significant difference in A1C reduction between IPT and MDI at any point during follow-up. Of note, the initial improvement in glycemic control after 3 months of initiation of pump therapy was not sustained throughout the year-long study period. The authors postulated that the initial improvement in glycemic control could be related to more frequent contact with the

diabetes care team, improved parent and caregiver attention to diabetes care because of use of novel technology, a Hawthorne effect after study entry, or a combination of these.

Children and adolescents

As already mentioned above, two reviews[31,38] contained meta-analyses for children (including preschool children, children, and adolescents) and found that, compared to MDI, IPT yielded an additional reductions in A1C levels by 0.2% to 0.24%, but these differences are not considered clinically significant.

Two new RCTs[22,44] conducted in children and adolescents demonstrated a reduction in A1C levels over time in both groups from baseline but did not find any statistically significant differences in A1C reduction between the two treatment groups.

One of the RCTs[22] conducted in newly diagnosed children and adolescents suggested that one of the reasons for no difference between the two groups might be that the MDI group used five to six daily injections (compared to earlier studies using only one or two injections). The authors offered some explanations for the lack of the difference between IPT and MDI, which include:

1. there is a similar effectiveness on glycemic control between the two treatment regimes,
2. the study period might be too short to detect a difference in outcome because many patients could have had a remission phase that lasted for some time into the study, or
3. the study did not set any specific target for blood glucose level or A1C apart from "as good metabolic control as possible".

A tighter target for A1C may have been easier to accomplish with IPT, thereby differentiating in effectiveness between the two treatment methods.

Pregnant women

Of the two systematic reviews[32,39] on pregnant women, the review that included six RCTs published between 1986 and 1993[39] found that A1C levels reduced in both groups from the first trimester to term; however, a meta-analysis of three RCTs did not show any differences in A1C levels between the two treatment groups at any time period.

Use of insulin analogues

As shown in Table T.D.5, for MDI, most of the six new RCTs used rapid-acting insulin analogues (insulin lispro or insulin aspart) for bolus injection and two studies used long-acting insulin analogue (insulin galrgin) for basal injection. The most recent RCT[42] did not find any difference between IPT and MDI groups despite the fact that both groups used insulin analogues.

Table T.12: Glycemic control during IPT compared with MDI in patients with T1DM

Patient group	**A1C pooled weighted mean difference** (95% confidence interval)*							
	SR 1[31]	**SR 2[34]**	**SR 3[35]**	**SR 4[36]**	**SR 5[37]**	**SR 6[38]**	**SR 7[32]**	**SR 8[39]**
Adults	–0.19 (–0.27, –0.11)**	All patients (including three age groups): with insulin lispro: –0.2 (–0.4, –0.1)** with insulin aspart: –0.6 (–1.0, –0.2)**; For mean age > 10 yrs: –0.3 (–0.4, –0.2)**; For mean age ≤ 10 yrs: –0.1 (–0, –0.3)**	All patients (including adults and children and adolescents): –0.21 (–0.13, –0.3)**	–0.4 (–0.65, –0.2)**	—	—	—	—
Pre-school children	–0.20 (–0.43, –0.03)**			Significantly lower in IPT group	No pooling; no difference between IPT and MDI groups	–0.24 (–0.41, –0.07)**	—	—
Children/ Adolescents				Slightly higher in IPT group (nss)	—		—	—
Pregnant women	—	—	—	—	—	—	No pooling; no difference between IPT and MDI groups	0.10 (–0.12, 0.33) (nss)

Abbreviations: IPT: insulin pump therapy; MDI: multiple daily injection; nss: not statistically significant; RCTs: randomized controlled trials; SR: systematic review; T1DM: type 1 diabetes

*Negative values favour IPT; **statistically significant

A dash (—) indicating that patient group was not included

Table T.13: Changes in A1C levels reported in six new RCTs

Study	Differences between IPT and MDI*	Patients	Basal-bolus insulins
Adult patients			
Bolli et al. 2009[42] N = 50	**Follow-up**: 5.6 months **A1C** (%): –0.1 at 5.6 months (nss)	**Baseline A1C** (mean, %): 7.7 in IPT vs. 7.8 in MDI **History of SH**: none (exclusion: patients with > two SH episodes in the past 6 months)	**IPT**: insulin lispro **MDI**: insulin glargine/insulin lispro
Peyrot & Rubin 2009[6] N = 28	**Follow-up**: 3.7 months **A1C** (%): –0.7 at 3.7 months (nss)	**Baseline A1C** (%): 8.6 (all patients) **History of SH**: NA	**IPT**: unclear **MDI**: unclear
Thomas et al. 2007[28] N = 21	**Follow-up**: 5.6 months **A1C** (%): –0.1 at 5.6 months (nss)	**Baseline A1C** (%): 8.5 in IPT vs. 8.6 in MDI **History of SH**: all patients (inclusion: patients with ≥ one SH episodes in the past 6 months)	**IPT**: insulin lispro **MDI**: insulin glargine/insulin lispro
Preschool children			
Nabhan et al. 2009[43] N = 42	**Follow-up**: 12 months **A1C** (%): –0.2 at 6 months (nss)	**Baseline A1C** (%): 9.0 in IPT vs. 9.0 in MDI **History of SH**: NA	**IPT**: insulin lispro **MDI**: NPH, lente, or glargine/insulin lispro
Children and adolescents			
Nuboer et al. 2008[44] N = 38	**Follow-up**: 3.5 months **A1C** (%): –0.16 at 3.5 months (statistical significance unknown)	**Baseline A1C** (%):7.7 in IPT vs. 8.0 in MDI **History of SH**: in 10 of 38 patients (inclusion: a history of repeated symptomatic hypoglycemia)	**IPT**: insulin aspart **MDI**: NPH or insulin glargine/insulin aspart or regular insulin
Skogsberg et al. 2008[22] N = 72	**Follow-up**: 24 months **A1C** (%): 0 at 24 months (nss)	**Baseline A1C** (%): 8.2 in IPT vs. 8.4 in MDI **History of SH**: none	**IPT**: insulin lispro/insulin lispro **MDI**: insulin glargine/insulin lispro

Abbreviations: glycated hemoglobin; IPT: insulin pump therapy; MDI: multiple daily injections; N: total number; NA: not available; NPH: neutral protamine Hagedorn; nss: not statistically significant; RCTs: randomized controlled trials; SH: severe hypoglycemia; T1DM: type 1 diabetes
*Negative values favour IPT

Dependence of outcomes on patient characteristics

Currently available research evidence from the included systematic reviews and new RCTs is insufficient to demonstrate any association between the outcome on glycemic control and various patient characteristics, including age, baseline A1C levels, duration of diabetes, or a history of severe hypoglycemia.

Dependence of outcomes on training, support, and expertise

The best quality systematic review[31] found that the included studies had widely varying protocols for training their participants in insulin management with IPT and MDI. Information was extracted from new RCTs regarding the training and education provided to patients or parents of children as well as special equipment required for initiating IPT (Table T.D.5). In general, the patients treated with IPT received enhanced training, education, and support from diabetes care teams in comparison with the MDI control group.

A subgroup analysis performed within the best quality systematic review[31] did not reveal any difference in endpoint A1C or hypoglycemia risk based on differences in training. In addition, a new RCT[43] on preschool children found that an initial improvement in glycemic control after 3 months of IPT was not sustained throughout a year-long study period. This could be related to better support from the diabetes team and improved parent and caregiver attention to diabetes care at the beginning of the study. Thus, currently available evidence is insufficient to establish the relationship between the outcomes of IPT and factors such as training or education, support from the diabetes care team, and expertise and experience of care providers.

Patient satisfaction and quality of life

Patient satisfaction with the treatment for diabetes can be measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ),[48] and quality of life (QoL) can be measured by the Audit of Diabetes-Dependent Quality of Life (ADDQoL). It is noteworthy that improved patient satisfaction with the treatment may be an important influence on QoL, but it cannot be interpreted as improvement of overall QoL. An understanding of the effect of diabetes on QoL requires broader coverage of life aspects likely to be influenced by the condition, its treatment, and any complications.[48]

Adults

Findings from systematic reviews: None of the four systematic reviews on adult patients with T1DM assessed patient satisfaction with the treatments or QoL.

Findings from new RCTs: None of the three RCTs in adult patients measured both patient satisfaction and QoL. Two RCTs[6,42] found improved patient satisfaction with IPT compared to MDI but did not report on QoL outcomes. One RCT[28] with 21 patients found no difference between the treatment groups in any QoL measures.

Preschool children

Findings from systematic reviews: One review[37] that included three RCTs found that two RCTs used modified version of the Diabetes Quality of Life (DQoL) survey and showed improvement in QoL scores following IPT.

Findings from new RCTs: The only new RCT[43] in preschool children found that children and families were pleased with IPT evidenced by low discontinuation rate (at the end of the 6-month study period, 95% families opted to continue IPT); however, this study did not measure QoL.

Children and adolescents

Findings from systematic reviews: One systematic review[38] reported significantly higher patient satisfaction with IPT in one study but found no difference between IPT and MDI in QoL measures in another study.

Findings from new RCTs: None of the two RCTs in this group reported both patient satisfaction and QoL outcomes. One study[22] found a significant higher patient satisfaction with IPT compared to MDI. The other study[44] found improved QoL with both IPT and MDI but no significant difference between the two treatment groups.

Pregnant women

None of the two systematic reviews[32,39] reported any patient satisfaction or QoL outcomes in pregnant women treated with IPT or MDI.

Secondary complication of diabetes

Almost all of the included studies did not assess this outcome as RCTs are usually conducted in a relatively short period. Only one review[39] on pregnant women reported higher rates of worsening retinopathy in the IPT group, but the difference was not statistically significant.

Neuro-cognitive, parenting, and child behaviour measures

Only one new RCT[43] assessed neuro-cognitive, parenting, and child behaviour changes in preschool children. It found no statistically significant differences between the IPT and MDI groups.

Pregnancy outcomes

The two systematic reviews[32,39] did not find any differences in pregnancy outcomes in pregnant women treated with IPT or MDI.

Summary

Overall, evidence from the included systematic reviews and new RCTs indicate that both IPT and MDI resulted in significant reductions in A1C from baseline levels. However, when compared to MDI, IPT yielded only a slightly greater reduction in A1C levels (less than 0.5% in most cases), which was not considered clinically significant. This finding was similar across different patients groups. Although some studies showed that patient satisfaction with IPT was higher than with MDI, information about QoL following IPT is very limited. Limited evidence from two systematic reviews did not indicate any significant differences in pregnancy-related outcomes between the two treatment groups.

The relative efficacy of IPT versus MDI in patients with poor glycemic control and those with a history of recurrent or severe hypoglycemic and hypoglycemia unawareness remains unclear. The impact of the slightly better glycemic control with IPT compared to MDI on long-term complications remains to be determined.

Conclusions from HTA reports

The Medical Advisory Secretariat of the Ontario Ministry of Health and Long-Term Care published an HTA report[40] that focuses on adult patients with T1DM or T2DM. This report found that in adult patients with T1DM, compared to MDI, IPT confers a statistically significant but not clinically significant (defined as A1C of 1.0%) reduction in A1C levels. There is conflicting evidence regarding both mild and severe hypoglycemia in this population. There is an improved quality of life; however, limitations exist with this evidence.

The Health Services Assessment Collaboration in New Zealand conducted an update[41] of the 2004 NHS technology assessment report[45] and searched for RCT studies published between 2002 and August 2007. This 2008 update report concluded that when compared with optimized MDI, IPT results in a modest but potentially worthwhile improvement in A1C levels in adults and children and

adolescents with T1DM. Because of the short duration of the clinical trials, it is not possible to evaluate the longer term benefits of such a difference in A1C levels; however, there is an expectation that it would be reflected in a reduction in long-term complications. Although more immediate primary benefits from IPT may be associated with an impact on the incidence of severe hypoglycemic events and improved quality of life (through greater flexibility of lifestyle), there is limited evidence to support this from the studies identified in this update.

Clinical practice guidelines and position statements

Several clinical practice guidelines addressed the potential role of IPT in the treatment of patients with T1DM (Table T.14).

For adult patients

The Canadian Diabetes Association 2008 guidelines[7] recommended MDI or IPT as the treatment of choice to achieve glycemic targets in adult patients with T1DM but did not mention younger patients. This recommendation was based on the results of DCCT published in 1993. Based on the findings from two RCTs, the guidelines recommended that insulin aspart or insulin lispro be used for IPT in adult patients with T1DM.

According to the 2008 NICE guidelines *Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus*, IPT is recommended as a treatment option for adults with T1DM provided that attempts to achieve target A1C levels with MDIs result in the patient experiencing disabling hypoglycemia, or A1C levels have remained high (i.e., 8.5% and above) on MDI therapy (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care.[13] IPT should be initiated only by a trained specialist team consisting of a physician with a special interest in IPT, a diabetes specialist nurse, and a dietitian. The specialist team should provide structured education programs and advice on diet, lifestyle, and exercise appropriate for patients using insulin pumps.[13]

For children and adolescents

In the NICE 2008 guidelines,[13] in addition to adult patients with T1DM, IPT was also considered appropriate for younger patients between 12 and 18 years as well as for children younger than 12 years. No level of evidence for this recommendation was provided.

A consensus statement from the European Society for Pediatric Endocrinology, Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes,[15] recommended that "all pediatric patients with T1DM are potential candidates for IPT, and there is no lower age limit for initiating IPT". This recommendation for initiating IPT was based on expert consensus or clinical experience. The decision to begin pump therapy should be made jointly by the child, his or her parent(s) or guardians, and the diabetes team. A pediatric multidisciplinary diabetes team experienced in IPT is required to initiate IPT and supervise the ongoing management of a child on IPT.

This consensus statement[15] recommended that IPT be considered in the conditions listed below:

- Recurrent severe hypoglycemia
- Wide fluctuations in blood glucose levels regardless of A1C
- Suboptimal diabetes control (i.e., A1C exceeds target range for age)
- Microvascular complications, risk factors for macrovascular complications, or both

- Good metabolic control but insulin regimen that compromises lifestyle

Other circumstances in which IPT may be beneficial include:

- young children and especially infants and neonates,
- adolescents with eating disorders (based on expert consensus),
- children and adolescents with a pronounced dawn phenomenon (based on expert consensus),
- children with needle phobia (based on expert consensus),
- pregnant adolescents, ideally preconception,
- ketosis-prone individuals, and
- competitive athletes (based on expert consensus).

According to the 2005 Australian guidelines,[49] IPT should be considered as a treatment option for children and adolescents with T1DM. This recommendation was based on evidence from systematic reviews of relevant RCTs. IPT should be initiated and supervised by a specialized multidisciplinary team trained in pump therapy in children and adolescents with diabetes.

For pregnant women

A NICE guideline report prepared by the National Collaborating Centre for Women's and Children's Health[50] entitled *Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period* recommended that "during pregnancy, women with insulin-treated diabetes should be offered continuous subcutaneous insulin infusion if adequate glycemic control is not obtained by multiple daily injections of insulin without significant disabling hypoglycemia." This recommendation was based on evidence from a Cochrane systematic review[32] of two RCTs and three other RCTs that were included in another systematic review[39] on pregnant women. Both of these reviews are included in the present report.

Other

The American Diabetes Association[51] position statement entitled *Standards of medical care in diabetes-2009* recommended that therapy for T1DM consist of:

1. use of multiple dose insulin injections (three to four injections per day of basal and prandial insulin) or IPT;
2. matching of prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity; and
3. for many patients (especially if hypoglycemia is a problem), use of insulin analogs.

Target patient groups (adults or children and adolescents) were not specified for these recommendations. Furthermore, no sources and grades of evidence were provided for these recommendations.

Table T.14: Recommendations from clinical practice guidelines

Guidelines	Recommendations
For adult patients	
Canadian Diabetes Association 2008[7]	• To achieve glycemic targets in adults with T1DM, MDI (basal-prandial insulin) or the use of IPT as part of intensive diabetes management regimen is the treatment of choice • Insulin aspart or insulin lispro should be used when IPT is used in adults with T1DM
National Institute for Health and Clinical Excellence 2008[13]	• A treatment option for adults provided that attempts to achieve target A1C levels with MDI results in repeated and unpredictable occurrence of hypoglycemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life, or A1C levels have remained high (≥ 8.5%) on MDI therapy despite a high level of care
For children and adolescents	
National Institute for Health and Clinical Excellence 2008[13]	• A treatment option for adults and children 12 years and older with T1DM provided that attempts to achieve target A1C levels with MDI results in repeated and unpredictable occurrence of hypoglycemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life, or A1C levels have remained high (≥ 8.5%) on MDI therapy despite a high level of care • A treatment option for children younger than 12 years with T1DM provided that MDI therapy is considered to be impractical or inappropriate, and children on insulin pumps would be expected to undergo a trial of MDI therapy between the ages of 12 and 18 years
European Society for Pediatric Endocrinology, Lawson Wilkins Pediatric Endocrine Society, International Society for Pediatric and Adolescent Diabetes 2007[15]	• All pediatric patients with T1DM are potential candidates for IPT • There is no lower age limit for initiating IPT
For pregnant women	
National Institute for Health and Clinical Excellence 2008[50]	During pregnancy women with insulin-treated diabetes should be offered continuous subcutaneous insulin infusion (CSII, or IPT) if adequate glycemic control is not obtained by multiple daily injections of insulin without significant disabling hypoglycemia (defined as repeated and unpredicted occurrence of hypoglycemia requiring third-party assistance that results in continuing anxiety about recurrence and is associated with significant adverse effect on quality of life)

Abbreviations: A1C: glycated hemoglobin; CSII: continuous subcutaneous insulin infusion; IPT: insulin pump therapy; MDI: multiple daily injections; T1DM: type 1 diabetes

Discussion

Assessment limitations

The present report builds on the evidence from a 2008 systematic review[31] that included 13 RCTs on patients with T1DM published between 2002 and March 2008. This review with a good quality rating focused on hypoglycemia and glycemic control but did not report on other safety outcomes such as diabetes ketoacidosis, infections, or pump malfunction, nor other efficacy outcomes such as quality of life. The meta-analysis of the safety outcome, severe hypoglycemia, was performed only for the whole population regardless of age. Although pooled weighted mean differences in A1C levels were available for adults and children, no further subgroup analysis was conducted for preschool children only or for children and adolescents only. Furthermore, this review excluded pregnant women with diabetes. Therefore, evidence on these subgroups of patients had to be sought from other systematic reviews or results of newly published RCTs, which are small in quantity (only six in total) and unclear in methodological quality with insufficient reporting of randomization processes.

Time permitting, a meta-analysis could have been performed to incorporate the results from these six new RCTs into the 2008 meta-analysis. However, because a lack of significant differences in terms of severe hypoglycemia and reductions in A1C levels was reported in most of the six RCTs (most of them used insulin analogues for MDI), an updated meta-analysis would be unlikely to dramatically change the overall conclusion about the safety and efficacy of IPT compared to MDI.

A systematic review may be subject to a variety of biases, such as those seen in the included original studies as well as those specifically related to the systematic review process itself (e.g., publication bias, language bias, inclusion bias, or outcome reporting bias).[52] In the present report, only data published in peer-reviewed (publication bias) and English-language (language bias) journals are included, which may have led to an overestimate of the treatment effects as usually positive results are more likely to be published in this way.

Information on safety (adverse effects or complications of IPT or MDI) and long-term complications of diabetes was obtained only from the included systematic reviews of RCTs or new RCTs, which usually only enrolled a small number of participants and had relatively short periods of follow-up. Information from other types of studies, such as cohort and case-control studies, uncontrolled trials, case series, and case reports, was not sought due to time constraints. This may have resulted in an underreporting of adverse events or complications of the treatments.

Authors of the six new RCTs were not contacted for missing information or for clarification because of time constraints. This may have impacted the quality assessment and consequently increased the uncertainty about the validity of the included studies.

Dependence of outcomes on patient characteristics

Some of the suggested characteristics that may increase the likelihood of success with IPT in children and adolescents were listed as follows:[53]

- Motivation factors include:
    - seeking to lower glucose and A1C,
    - seeking to reduce risk of hypoglycemia,
    - seeking to improve lifestyle, and

    - interest in trying this approach to insulin treatment.
- Treatment factors include:
    - a history of good self-management skills and reliable follow-up,
    - the ability to perform carbohydrate counting,
    - performing four or more blood glucose tests per day,
    - adequate control with injection therapy,
    - reliable adult supervision,
    - the ability to master technical aspects of pump therapy, and
    - active communication with the diabetes team.

However, limited subgroup analyses failed to reveal any association between patient characteristic and the outcomes.

Gaps in evidence

The authors of the best quality review[31] pointed out several limitations of the currently available evidence. The paucity of evidence on patients with T1DM who were at high risk of severe hypoglycemia (i.e., recurrent severe hypoglycemia or hypoglycemia unawareness) precluded further analysis of the impact of treatment on severe hypoglycemia. Many studies were conducted at centres with extensive experience in pump therapy, which raises the question of whether academic centres having an interest in improving MDI therapy may have had a different effect. The magnitude of association between pump manufacturer funding or financial ties with authors and trial results could not be ascertained because of the lack of sufficient independent trials, which has even greater relevance in view of the inherent inability of investigators and patients to remain blind to the treatment assignment, resulting in a greater susceptibility to bias.[31]

According to the authors, although ongoing multicentre trials are currently comparing MDI with current insulin pumps for patients with T1DM, the lack of standardized and prompt reporting of hypoglycemia presents a methodological limitation for future research. Patients need to report hypoglycemia in real time, enhancing the quality and completeness of this outcome and promoting clinical investigation and intervention to prevent further hypoglycemia. Clinical trial protocols and reports should also standardize the way they report hypoglycemia outcomes. The authors suggested that, in addition to reporting measures of central tendency and variance, investigators should also report the number of patients experiencing no, few, several, and many episodes of severe to nocturnal hypoglycemia.[31]

Almost all of the included RCTs in this review reported conflict of interest between authors and insulin pump manufacturers who provided material or financial support. Whether this conflict of interest had any tangible influence on glycemic and hypoglycemic outcomes could not be determined. More independent RCTs without relying on manufacturer assistance should be conducted in the future.

Overall, most of the six new RCTs included in this report suffered from limited power of study and short durations of follow-up. Furthermore, there is a lack of new studies on pregnant women with T1DM. Future research should address these limitations.

Implementation considerations

Delivery considerations

The use of insulin pumps poses significant challenges at different age groups, with each group requiring different levels of provider expertise and training protocols.[31] An adequate education program should include blood monitoring, technical aspects, prevention of cutaneous complications, management of hyper- and hypoglycemia, prevention of diabetes ketoacidosis, and management of interruption of the insulin pump.[25]

Additional resources

As mentioned in the six new RCTs (Appendix T.D, Table T.D.5), use of insulin pumps requires other equipment such as blood glucose monitors and a central laboratory equipped with high-performance liquid chromatography for measuring A1C level.

Impacts on Alberta health system

IPT is considered the most intensive type of diabetes management, and before transitioning, consideration of regimen benefits should include lifestyles and quality-of-life issues in addition to medical benefits.[54]

Use of insulin pumps in patients with T1DM requires support from a multidisciplinary diabetes care team with expertise on IPT. Appropriate patient subgroups that would benefit from IPT compared to MDI could not be identified based on the clinical outcomes reported in the included studies.

Conclusions

Evidence from the eight systematic reviews, two HTAs, and six new RCTs indicates that IPT is as safe as MDI in terms of the frequency of severe hypoglycemia episodes and diabetic ketoacidosis in adult patients, preschool children, children and adolescents, and pregnant women. The pooled results for severe hypoglycemia from the best quality systematic review did not demonstrate any significant differences between the two treatment groups. Insulin infusion site infections and pump malfunctions were reported in some studies, but most of them did not result in serious clinical consequences.

In terms of glycemic control, evidence from the included studies indicates that both IPT and MDI resulted in significant reductions in A1C from baseline levels. However, when compared to patients receiving MDI, patients receiving IPT had slightly lower A1C levels, which were statistically significant but not clinically significant. This finding was similar across all age groups (adults, preschool children, and children and adolescents). Limited evidence did not reveal any significant difference in A1C reduction between IPT and MDI in pregnant women.

The available data generally indicate a higher patient satisfaction with IPT; however, information on QoL is very limited. The two reviews on pregnant women also failed to find any difference in pregnancy-related outcomes between the two treatment groups.

Neuro-cognitive dysfunction and behavioural changes were measured in only one new RCT on preschool children and no significant differences were found between the IPT and MDI treatment groups.

As the included studies are generally of short durations (less than 2 years) of follow-up, none of the studies reported long-term outcomes such as changes in the secondary complications of diabetes (e.g., retinopathy, cardiovascular, renal, or neurologic diseases).

The included studies with small sample sizes and short durations of follow-up may not allow sufficient power to detect treatment effects. The impacts of various factors on the treatment effects, such as types of insulin, inclusion of patients with previous severe hypoglycemia, difference in training and education of patients and of expertise or experience of care providers, or difference in study quality, require further exploration.

Although several advantages with the use of insulin pump over MDI have been proposed for patients with T1DM, including the improvement in glycemic control and the reduction in severe hypoglycemia episodes, the currently available evidence failed to demonstrate the superiority of IPT over MDI. Superiority of one treatment over the other in terms of the frequency of severe hypoglycemia episodes and the magnitude of A1C reduction for all age groups, including pregnant women, was not supported by the current research evidence. In particular, there is a lack of studies that included patients with a history of recurrent severe hypoglycemia or hypoglycemia unawareness while on MDI, which is one of the primary indications for IPT. Currently available research evidence based on clinical outcomes is insufficient to identify appropriate patient subgroups that would benefit from IPT and to establish appropriate criteria for initiating it.

Summary

T1DM, characterized by high blood glucose levels that require lifelong insulin therapy, can cause short- and long-term complications in different organs such as the heart, eyes, kidneys, and blood vessels. It may cause neuro-cognitive dysfunction and behavioural changes in children. In pregnant women high glucose levels are associated with increased risk of fetal congenital malformation, peri-natal mortality, obstetric complications, and neonatal morbidity.

Results from the Diabetes Control and Complication Trial (DCCT), a large multicentre trial that involved 1441 patients from 29 centres, confirmed that, compared to conventional insulin therapy (one or two daily insulin injections), intensive insulin therapy through either MDI (defined as three or more injections per day) or IPT are associated with improved glycemic control and decreased secondary complications of diabetes.

However, intensive insulin therapy is associated with a higher risk for hypoglycemia compared with conventional insulin therapy. About one-third of the patients under intensive insulin therapy experience severe hypoglycemia (defined as hypoglycemia episodes where a third party is required for assistance), and about 5% of these patients account for half of all severe hypoglycemia episodes. Severe hypoglycemia presents a major barrier for patients with T1DM to achieve optimal glycemic control.

Currently MDI is the most commonly used method for delivering intensive insulin therapy. Conventionally MDI consists of three or more daily injections of regular human insulin and NPH insulin by syringes or pens. In recent years a basal-bolus approach that combines long-acting insulin glargine or insulin detemir with pre-meal injections of rapid-acting insulin analogues has emerged as the "gold standard" for intensive MDI therapy in adult patients with T1DM.

An insulin pump is a complex computerized electronic device used for continuous subcutaneous insulin infusion. IPT consists of a basal-bolus injection, i.e., continuous infusion of low-dose rapid-acting insulin analogues (such as insulin lispro or insulin aspart) and pre-meal bolus injections of rapid-acting insulin analogues. Various pump models supplied by three main insulin pump manufacturers, including Animas Canada, Disetronic Medical Systems, and Medtronic of Canada, are available on the Canadian market with licence approval from Health Canada.

IPT is the closest to the physiologic method of insulin delivery currently available and offers the possibility of more flexibility and more precise insulin delivery than MDI. It has been proposed that IPT may have some advantages over MDI. Compared to MDI, one major potential benefit of IPT is a reduction of glycemic variability through tighter, more precise glycemic control, which decreases the risk for micro- and macrovascular complications. Another postulated important benefit of IPT over MDI is a reduction of severe hypoglycemic events by delivering small doses of subcutaneous insulin throughout the day that can be adjusted based on patient-specific requirements.

The **T**echnology section of the report attempts to examine the research evidence on the safety and efficacy of IPT compared to MDI in the following four patient groups:

- adults (19 years and older),
- preschool children (0 to 6 years),
- children and adolescents (7 to 18 years), and
- pregnant women.

Through a comprehensive literature search eight recent systematic reviews, two HTAs, and six new RCTs were included in this report. Findings from these studies are used to form the evidence base for the safety and efficacy of IPT as compared to MDI.

Of the eight systematic reviews, four included patients of all ages (adults, preschool children, and children and adolescents), one review focused on preschool children only, and one included preschool children as well as children and adolescents. The other two reviews included only pregnant women with diabetes; indeed, these two reviews included six RCTs in total, five with a target population of pregnant women with T1DM.

Using a methodological quality assessment tool for systematic reviews, two reviews were rated as "good", one as "poor", and the other five as "average". This Technology report builds on one of the good quality reviews[31] that included only the most recent RCTs, those published between 2002 and March 2008.

Six new RCTs published between 2007 and 2009 were not included in any of the identified systematic reviews or HTAs. Three RCTs included 99 adult patients, one included 42 preschool children, and the other two RCTs included 110 children and adolescents. No new RCTs were found that enrolled pregnant women with T1DM. The two systematic reviews on IPT in pregnancy included RCTs published more than 10 years ago (from 1986 to 1993). Thus, the lack of new RCTs makes it impossible to examine the safety and efficacy of newer generations of insulin pumps as well as insulin analogues in this group of patients.

Using the Cochrane risk of bias tool for the assessment of the RCTs, all six new RCTs were judged to have "unclear" to "high" risk of bias. The major problem with most of these studies is that there is insufficient reporting of the randomization process, which raises the question of whether a true randomization was attained in these trials. One of the limitations with the present report is that the authors of these studies were not contacted for clarification due to time constraints.

The reported results from the eight systematic reviews, two HTAs, and six new RCTs provide evidence that IPT is as safe as MDI in terms of frequency of severe hypoglycemia (abnormally low blood glucose levels) episodes and diabetic ketoacidosis (abnormally high blood glucose levels) for adult patients, preschool children, children and adolescents, and pregnant women. The pooled results for severe hypoglycemia from the best quality systematic review did not demonstrate any

significant differences between the two treatment groups, although some individual studies suggested a lower frequency of this outcome in patients treated with IPT. Insulin infusion site infections and pump malfunctions were reported in some studies, but most of these did not result in serious clinical consequences.

Overall, evidence from the eight systematic reviews, two HTAs, and six new RCTs indicates that both IPT and MDI resulted in significant reductions in A1C from baseline levels. However, when compared to MDI, IPT yielded only a slightly higher reduction in A1C levels. This finding was similar across all age groups (adults, preschool children, and children and adolescents). Limited evidence did not reveal any significant difference in A1C reduction between IPT and MDI in pregnant women.

One of the important outcomes, quality of life (QoL), was not frequently assessed in the included systematic reviews and was measured in only two new RCTs, with conflicting results. Patient satisfaction, although not a direct measure of QoL, was found to be higher in patients treated with IPT. The two reviews targeting pregnant women also failed to find any differences in pregnancy-related outcomes between the two treatment groups.

Neuro-cognitive dysfunction and behavioural changes were measured in only one new RCT[43] on preschool children, and no significant difference was found between the IPT and MDI treatment groups.

As the included studies are generally of short durations (less than 2 years) of follow-up, none of the studies reported long-term outcomes such as changes in the secondary complications of diabetes (e.g., retinopathy, cardiovascular, renal, or neurologic diseases).

The included studies with small sample sizes and short durations of follow-up may not allow sufficient power to detect treatment effects. The impacts of various factors on the treatment effects, such as types of insulin, inclusion of patients with previous severe hypoglycemia, difference in training or education of patients and expertise or experience of care providers, or difference in study quality, require further exploration.

In conclusion, although several advantages with the use of insulin pump over MDI have been proposed for patients with T1DM, including the improvement in glycemic control and the reduction in severe hypoglycemia episodes, the currently available evidence failed to demonstrate the superiority of IPT over MDI in terms of the frequency of severe hypoglycemia episodes and the magnitudes of A1C reduction for all age groups, including pregnant women. In particular, there is a lack of studies that included patients with a history of recurrent severe hypoglycemia or hypoglycemia unawareness while on MDI, which is one of the primary indications for IPT. Currently available research evidence based on the clinical outcomes is insufficient to identify appropriate patient subgroups that would benefit from IPT and to establish appropriate criteria for initiating IPT.

Appendices

Appendix T.A: Methodology

Search strategy

The search was conducted by an IHE information specialist. The preliminary search was done to retrieve articles published from 2004 to February 2009. The search was further limited to English-language articles only and to systematic reviews and HTAs. The searches were updated 16 June 2009.

The search strategy for RCTs combines updates of two previously published systematic reviews (literature published since 2006) with searching in additional databases (CINAHL, Web of Science, and Biosis Previews) for literature published within the past 10 years. No language restrictions were applied to the search.

Medical Subject Headings (MeSH) terms relevant to this topic are: Insulin Infusion Systems, Infusion Pumps, and Diabetes Mellitus.

Other key search terms included T1DM, insulin therapy, insulin pump, multiple daily injection, safety, efficacy, effectiveness, glycemic control, hypoglycemia, and quality of life. We did not contact any experts regarding key search terms, nor did we conduct handsearching because of time constraints.

Table T.A.1: Search strategy[a]

Database	Edition or date searched	Search for RCTs	Search for systematic reviews
Core Databases			
The Cochrane Library http://www.thecochranelibrary.com	16 June 2009	""insulin pump*" or "insulin infusion*" or CSII or IPT or "subcutaneous insulin" in Title, Abstract or Keywords and diabet* in Title, Abstract or Keywords, from 2006 to 2009 in Cochrane Central Register of Controlled Trials" NOT "type 2":ti,ab,kw not "type 1" AND "type 2":ti,ab,kw	continuous or pump* or infusion* or IPT or CSII in Title, Abstract, or Keywords and insulin in Title, Abstract or Keywords and diabet* in Title, Abstract, or Keywords, from 2004 to 2009
MEDLINE (OVID interface)	16 June 2009	1 Insulin Infusion Systems/ 2 infusion pumps/ or infusion pumps, implantable/ 3 (insulin or novorapid or humalog or apidra or humulin$ or novolin or levemir or lantus).mp. 4 exp Infusions, Parenteral/ 5 3 and (2 or 4) 6 Administration, Cutaneous/ 7 exp Insulin/ 8 6 and 7	1 Insulin Infusion Systems/ 2 infusion pumps/ or infusion pumps, implantable/ 3 insulin.mp. 4 exp Infusions, Parenteral/ 5 3 and (2 or 4) 6 Administration, Cutaneous/ 7 exp Insulin/ad [Administration & Dosage] 8 6 and 7 9 (insulin pump$ or insulin

		9 (insulin pump$ or insulin infusion$ or CSII).mp. 10 (subcutaneous adj2 insulin).mp. 11 (continuous adj2 insulin).mp. 12 ((closed-loop adj2 control) and (insulin or glucose)).mp. 13 1 or 5 or 8 or 9 or 10 or 11 or 12 14 exp Diabetes Mellitus, Type 1/ 15 diabet$.mp. and type 1.ti,ab. 16 diabetes mellitus/ or diabetes, gestational/ 17 or/14-16 18 (type 2 not (type 1 and type 2)).mp. 19 17 not 18 20 13 and 17 21 (Clinical trial or randomized controlled trial).pt. or randomi?ed.ti,ab. or placebo.ab. or exp clinical trial/ or comparative study/ or randomly.ab. or trial.ti. 22 20 and 21 23 limit 22 to yr="2006-Current" 24 (comment or editorial or historical article or letter or newspaper article).pt. 25 23 not 24 26 animals/ 27 humans/ 28 26 not (26 and 27) 29 25 not 28	infusion$).mp. 10 (subcutaneous adj2 insulin).mp. 11 (continuous adj2 insulin).mp. 12 1 or 5 or 8 or 9 or 10 or 11 13 exp Diabetes Mellitus/ 14 12 and 13 15 limit 14 to yr="2004 - 2009" 16 limit 15 to English language 17 meta-analysis.mp,pt. 18 (medline or pubmed).mp. 19 systematic$ review$.mp. 20 (technology assessment$ or hta).mp. 21 (search.mp. and review.pt.) or literature search.mp. 22 or/17-21 23 16 and 22
EMBASE (OVID interface)	16 June 2009 (to Week 24)	1 insulin pump/ 2 infusion system/ or infusion pump/ or continuous infusion/ 3 insulin infusion/ 4 Subcutaneous Drug Administration/ 5 (insulin or novorapid or humalog or apidra or humulin$ or novolin or levemir or lantus).mp. 6 (2 or 4) and 5 7 (subcutaneous adj2 insulin).mp. 8 (continuous adj2 insulin).mp. 9 (insulin pump$ or insulin infusion$ or CSII).mp. 10 ((closed-loop adj2 control) and (insulin or glucose)).mp. 11 1 or 2 or 6 or 7 or 8 or 9 or 10 12 exp Diabetes Mellitus/ 13 diabet$.mp. and type 1.ti,ab. 14 12 or 13	1 insulin pump/ 2 infusion system/ or infusion pump/ or continuous infusion/ 3 insulin infusion/ 4 Subcutaneous Drug Administration/ 5 insulin.mp. 6 (2 or 4) and 5 7 (insulin pump$ or insulin infusion$).mp. 8 (subcutaneous adj2 insulin).mp. 9 (continuous adj2 insulin).mp. 10 1 or 3 or 6 or 7 or 8 or 9 11 exp Diabetes Mellitus/ 12 diabetes.mp. 13 10 and (11 or 12) 14 limit 13 to (English language and yr="2004 - 2009")

		15 11 and 14 16 comparative study/ or intermethod comparison/ or drug comparison/ or controlled clinical trial/ or randomized controlled trial/ or (randomi?ed or randomly).ti,ab. or trial.ti. or double-blind$.mp. 17 15 and 16 18 (Type 2 not (type 1 and type 2)).ti,ab. 19 17 not 18 20 (exp vertebrate/ or animal/ or exp experimental animal/ or nonhuman/ or animal.hw.) not (exp human/ or human experiment/) 21 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. not (exp human/ or human experiment/) 22 20 or 21 23 19 not 22 24 limit 23 to yr="2006-Current"	15 meta analysis/ or "systematic review"/ 16 (medline or pubmed).mp. 17 (search$.mp. and review.pt.) or literature search.mp. 18 biomedical technology assessment/ 19 (technology assessment$ or hta).mp. 20 or/15-19 21 14 and 20 22 (editorial or erratum or letter or note).pt. 23 21 not 22
CRD Databases (DARE, HTA & NHS EED)	16 June 2009	Because the CRD Databases do not include records of RCTs, it was not searched for this part of the project.	1 MeSH Insulin Infusion Systems 2 MeSH Infusion Pumps EXPLODE 1 2 3 MeSH Infusions, Parenteral EXPLODE 1 4 MeSH Administration, Cutaneous 5 MeSH Insulin EXPLODE 1 2 6 insulin OR novorapid OR humalog OR apidra OR humulin* OR novolin OR levemir OR lantus 7 #2 OR #3 OR #4 8 #5 OR #6 9 #7 AND #8 10 "insulin pump" OR "insulin pumps" OR "insulin infusion" OR "insulin infusions" OR CSII OR "continuous insulin" OR "continuous subcutaneous" OR ipt 11 #1 OR #9 OR #10 12 MeSH Diabetes Mellitus

			EXPLODE 1 2 13 diabet* 14 #12 OR #13 15 #11 AND #14 16 #10 AND #14 RESTRICT YR 2004 2009
CINAHL	16 June 2009	1. ((MH "Infusion Pumps+") OR (MH "Infusions, Subcutaneous") OR (MH "Injections+")) and ((MH "Insulin+") OR (insulin or novorapid or humalog or apidra or humulin$ or novolin or levemir or lantus)) 2. "continuous insulin" or "continuous subcutaneous" or "insulin pump*" or "insulin infusion*" or IPT or CSII 3. 1 or 2 4. (MH "Diabetes Mellitus, Insulin-Dependent") OR (MH "Diabetes Mellitus") OR (MH "Pregnancy in Diabetes+") OR diabet* 5. 3 and 4 6. (randomized or randomised or randomly or double-blind) or TI trial* or PT Clinical trial 7. 5 and 6 limit to 1999-2009 8. "type 2" not ("Type 1" AND "type 2") 9. 7 NOT 8	This database was not included as part of the preliminary search for systematic reviews.
Web of Science	16 June 2009	#1 Topic=("insulin pump*" or "insulin infusion*" or CSII or IPT or "subcutaneous insulin") #2 Topic=diabet* #3 Topic=(randomized or randomised or randomly or double-blind or "controlled trial*" or "clinical trial*" or "comparative trial*") or TI=trial* #4 #1 AND #2 AND #3 Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=1999-2009 #5 Topic=("type 2") NOT Topic=("type 1" AND "type 2") #6 #4 NOT #5	This database was not included as part of the preliminary search for systematic reviews.
Biosis Previews	16 June 2009	#1 Topic=("insulin pump*" or "insulin infusion*" or CSII or IPT or "subcutaneous insulin") #2 Topic=diabet* #3 Topic=(randomized or randomised or randomly or double-blind or "controlled trial*" or "clinical trial*" or "comparative trial*") or TI=trial* #4 #1 AND #2 AND #3	This database was not included as part of the preliminary search for systematic reviews.

		Databases=PREVIEWS Timespan=1999-2009 #5 Topic=("type 2") NOT Topic=("type 1" AND "type 2") #6 #4 NOT #5	
PubMed	16 June 2009	#8 Search #6 NOT #7 #7 Search type 2 NOT (type 1 AND type 2) #6 Search #4 AND #5 #5 Search random* OR trial* or double blind* #4 Search #1 AND #2 AND #3 #3 Search in process[sb] OR pubmednotmedline[sb] OR publisher[sb] #2 Search diabet* #1 Search insulin pump* OR insulin infusion* OR CSII OR IPT OR subcutaneous insulin The search in PubMed was conducted to retrieve citations that were in process at the time of the search.	This database was not included as part of the preliminary search for systematic reviews.

[a] "*", "#", and "?" are truncation characters that retrieve all possible suffix variations of the root word; e.g., surg* retrieves surgery, surgical, surgeon, etc. Searches separated by semicolons have been entered separately into the search interface.

The search for grey literature was conducted 13 to 24 July 2009. The following is a list of the websites searched.

Table T.A.2: Grey literature search

Guidelines[a]
*CMA Infobase: http://www.cma.ca/index.cfm/ci_id/54316/la_id/1.htm
*TOP: http://www.topalbertadoctors.org/cpg.html
*National Guideline Clearinghouse: http://www.guideline.gov/
UK National Library for Health (NLH) Guidelines Finder: http://www.library.nhs.uk/guidelinesFinder
New Zealand Guidelines Group: http://www.nzgg.org.nz
Scottish Intercollegiate Guidelines Network: http://www.sign.ac.uk
Guidelines International Network: http://www.g-i-n.net
Guidelines Advisory Committee: http://www.gacguidelines.ca/index.cfm
UK NHS Clinical Knowledge Summaries: http://cks.library.nhs.uk
Theses Sources
Theses Canada Portal: http://www.collectionscanada.gc.ca/thesescanada/index-e.html
ProQuest Dissertations and Theses: Full Text (subscription database)
HTA Agencies
*AETMIS: http://www.aetmis.gouv.qc.ca/site/en_publications.phtml
*CADTH: http://www.cadth.ca/index.php/en/hta/reports-publications/search
Institute for Clinical and Evaluative Sciences (ICES): http://www.ices.on.ca/
Health Technology Assessment Unit at McGill: http://www.mcgill.ca/tau/
*Medical Advisory Secretariat: http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html
Technology Assessment at SickKids (TASK): http://pede.ccb.sickkids.ca/pede/task.jsp

WorksafeBC: http://www.worksafebc.com/health_care_providers/related_information/evidence_based_medicine/default.asp
ASERNIP-S: http://www.surgeons.org/asernip-s/
MSAC: http://www.msac.gov.au/
NZHTA: http://nzhta.chmeds.ac.nz/index.htm
Health Evidence Bulletins – Wales: http://hebw.uwcm.ac.uk
UK National Horizon Scanning Centre: http://www.pcpoh.bham.ac.uk/publichealth/horizon
UK NHS Health Technology Assessment Programme: http://www.ncchta.org
Centre for Clinical Effectiveness (CCE): http://www.mihsr.monash.org/cce/
ECRI HTAIS Database: http://www.ta.ecri.org/Topics/prod/home/new.aspx
Health Quality Council, Saskatchewan: http://www.hqc.sk.ca/
MHRA (Medicines and Healthcare Products Regulatory Agency) (UK): http://www.mhra.gov.uk
*NHS National Institute for Health and Clinical Excellence (NICE): http://www.nice.org.uk/
NHS Evidence: http://www.evidence.nhs.uk/
*EuroScan International Network: http://www.euroscan.org.uk/
California Health Benefits Review Program (CHBRP): http://www.chbrp.org/
California Technology Assessment Forum (CTAF): http://www.ctaf.org
Agency for Healthcare Research and Quality (AHRQ): http://www.ahrq.gov
NHS Centre for Evidence-based Purchasing: http://www.pasa.nhs.uk/PASAWeb/NHSprocurement/CEP
US VA Technology Assessment Program: http://www.va.gov/VATAP/publications.htm
Adelaide Health Technology Assessment (AHTA): http://www.adelaide.edu.au/ahta/pubs/2009/
City of Hamilton Effective Public Health Practice Project (EPHPP): http://old.hamilton.ca/phcs/ephpp/ReviewsPortal.asp
Health Evidence Network (HEN): http://www.euro.who.int/en/what-we-do/data-and-evidence/health-evidence-network-hen
Australia and New Zealand Horizon Scanning Network (ANZHSN): http://www.horizonscanning.gov.au
National Library of Medicine Health Services/Technology Assessment Text (HSTAT): http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
Aetna: http://www.aetna.com/cpb/cpb_menu.html
BlueCross BlueShield Technology Evaluation Center: http://www.bcbs.com/blueresources/tec/tec-assessments.html
Washington State Health Care Authority: http://www.hta.hca.wa.gov/assessments.html
Health Economics Resources
McMaster University, Centre for Health Economics and Policy Analysis: http://www.chepa.org
University of Technology Sydney, Centre for Health Economics Research and Evaluation: http://datasearch.uts.edu.au/chere/research/SearchPublication.cfm
Cost-Effectiveness Analysis (CEA) Registry: https://research.tufts-nemc.org/cear/default.aspx
Clinical Trials
NIH ClinicalTrials.gov (US): http://clinicaltrials.gov/
CenterWatch Clinical Trials Listing Service: http://www.centerwatch.com/
ClinicalStudyResults: http://www.clinicalstudyresults.org/
Current Controlled Trials (CCT): http://www.controlled-trials.com
Computer Retrieval of Information on Scientific Projects (CRISP): http://crisp.cit.nih.gov
Coverage, Regulatory, and Licensing Agencies
Alberta Health and Wellness: http://www.health.gov.ab.ca

Medical Devices Active Licence Listing (MDALL): http://www.mdall.ca/
US Food and Drug Administration (FDA): http://www.fda.gov
Drug Product Database: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php/
Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
Library catalogues
*NEOS catalogue: http://www.library.ualberta.ca/
AMICUS: http://www.collectionscanada.gc.ca/amicus/index-e.html
US National Library of Medicine Locator Plus: http://locatorplus.gov/
Websites
*Canadian Diabetes Association: http://www.diabetes.ca/
Manufacturers
Animas: http://www.animas.ca/; http://www.animascorp.com/
Insulet (maker of Omnipod): http://www.myomnipod.com/
Medtronic: http://www.medtronicdiabetes.ca/home.aspx?pagename=Home&language=English ; http://www.minimed.ca/; http://www.medtronic.com/ ; http://www.minimed.com/index.html
Disetronic Medical Systems: http://www.disetronic-ca.com/dstrnc_ca/; http://www.disetronic-usa.com/dstrnc_us/
Smiths Medical MD Inc.: http://www.smiths-medical.com/
Canadian Patient Advocacy group: Diabetes Advocacy: http://www.diabetesadvocacy.com/
Health Canada: http://www.hc-sc.gc.ca/index-eng.php
Google: http://www.google.ca

[a]Resource names preceded by an asterisk (*) indicate those sources that were reviewed as part of the preliminary search in February 2009, in addition to the full grey literature search in July 2009

Study selection

Inclusion criteria

Studies are included if they meet all of the following criteria.

Study design: systematic reviews/HTAs of RCTs, or RCTs

Note: An article was deemed to be a systematic review if it met all of the following criteria as defined by Cook et al. 1997:[47]

- focused clinical question;
- explicit search strategy;
- use of explicit, reproducible, and uniformly applied criteria for article selection;
- critical appraisal of the included studies;
- qualitative or quantitative data synthesis.

Population: patients with T1DM, no limit in terms of age, gender, pregnancy status, body mass index, comorbidities, and secondary complications of diabetes.

Intervention: IPT using human insulin or insulin analogues.

Comparator: MDI (three or more daily insulin injections) using human insulin or insulin analogues. Studies with more than one comparator were also included if the data were presented separately for an IPT verses MDI comparison.

Outcome of interest: at least one of the following:

- **Safety outcomes:** diabetic ketoacidosis, severe hypoglycemia, site infections, pump malfunction, etc.
- **Efficacy outcomes:** glycemic control (A1C level), patient satisfaction and quality of life, secondary complications of diabetes, neuro-cognitive function and behaviour changes in children if applicable; pregnancy outcomes if applicable

Clinical practice guidelines or position statements on the use of insulin pumps for the treatment of T1DM were also included in the report.

Exclusion criteria

Studies were excluded if they met any of the following criteria:

- **Study design:** nonrandomized comparative studies, case-control studies, case series studies, conference abstracts, letters, news, or editorial comments.
- **Population:** patients with T2DM, mixed group of patients with T1DM or T2DM without separate reporting of outcomes for each group, patients with T1DM who underwent islet transplantation or pancreas transplantation, women with gestational diabetes, patients with other acute conditions or diseases
- **Intervention:** intraperitoneal insulin pumps (implanted pump); peri-operative use of insulin pumps
- **Comparator:** comparison between different types of insulin pumps, different types of insulin analogues using the same insulin pumps, different glucose monitoring systems or devices using the same insulin pump, intravenous insulin infusion
- **Outcome measures:** technical aspects

Interrater agreement in study selection was not measured because of time constraints. Disagreements between the reviewers were resolved by discussion.

Data extraction

Data extraction from systematic reviews and HTAs

The following information was extracted by one researcher (BG) from the included systematic reviews and HTAs:

- **Study:** authors, year of publication, study objective
- **Search strategy:** search dates, list of databases, and other information sources
- **Study selection:** inclusion and exclusion criteria
- **Analytical method:** qualitative synthesis or meta-analysis
- **Included studies:** study characteristics and study quality

- **Results:**
  - **Safety:** diabetic ketoacidosis, severe hypoglycemia, infection, and pump malfunction
  - **Efficacy and effectiveness:** glycemic control (A1C level), patient satisfaction and quality of life measures (general health measures and diabetes specific measures), secondary complications of diabetes, pregnancy outcomes, neuro-cognitive function and behaviour changes in children
- **Authors' conclusions:** checked to ensure that conclusions matched study's results/findings

Data extraction from new RCTs

The following information was extracted by one researcher (BG) from the six RCTs:

- **Study:** author, year of publication, country where the study is conducted, single or multi-centre trial, study design, study objective, and aim
- **Patient:** age, gender distribution (male/female), duration of diabetes, baseline body mass index (BMI), baseline A1C levels, history of severe hypoglycemia, comorbidity (obesity, hypertension, hyperlipidemia, etc.), secondary complications of diabetes (cardiovascular disease, renal disease, retinopathy, neuropathy, etc.); patient inclusion or exclusion criteria
- **Intervention:** types of insulin pumps (name, manufacture), types of insulins used
- **Comparator:** types of delivery device used (syringe or pen), types of insulin used
- **Results and conclusions:**
  - **Safety:** diabetic ketoacidosis, severe hypoglycemia, infection, and pump malfunction
  - **Efficacy and effectiveness:** glycemic control (A1C level), treatment satisfaction and quality of life measures (general health measures and diabetes specific measures), secondary complications of diabetes, pregnancy outcomes, neuro-cognitive function and behaviour changes in children

Appendix T.B: Excluded studies

Table T.B.1: Excluded studies and reasons for exclusion

Excluded studies	Reason for exclusion
Excluded systematic reviews/HTAs	
Colquitt et al. Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. *Health Technology Assessment* (Winchester, England) 2004;8(43):iii-171.	Old review
Cote. Comparison of the insulin pump and multiple daily insulin injections in intensive therapy for type 1 diabetes. Available from: *http://www.aetmis.gouv.qc.ca/site/ en_publications_2004.phtml.*	Old review
Ludvigsson & Samuelsson. Continuous insulin infusion (CSII) or modern type of multiple daily injections (MDI) in diabetic children and adolescents a critical review on a controversial issue. *Pediatric Endocrinology Reviews* 2007;5(2):666-78.	Did not meet Cook criteria for SR
Nahata. Insulin therapy in pediatric patients with type 1 diabetes: continuous subcutaneous insulin infusion versus multiple daily injections. *Clinical Pediatrics* 2006;45(6):503-8.	Did not meet Cook criteria for SR
Pichon et al. *Diabetes mellitus treatment with insulin pump: clinical effectiveness – indications*. Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS); 2004.	Old review
Retnakaran et al. Continuous subcutaneous insulin infusion versus multiple daily injections: the impact of baseline A1C. *Diabetes Care* 2004;27(11):2590-6.	Old review
Siebenhofer et al. Meta-analysis of short-acting insulin analogues in adult patients with type 1 diabetes: continuous subcutaneous insulin infusion versus injection therapy. *Diabetologia* 2004;47(11):1895-1905.	Old review
Excluded randomized controlled trials	
Bin-Abbas et al. Comparison of insulin pump and multiple daily injection regimens in type 1 diabetic patients. *Current Pediatric Research* 2006;10(1-2):37-9.	Not an RCT
Bruttomesso et al. In type 1 diabetic patients with good glycaemic control, blood glucose variability is lower during continuous subcutaneous insulin infusion than during multiple daily injections with insulin glargine. *Diabetic Medicine* 2008;25(3):326-32.	Included in the best quality SR[31]
Cohen et al. Continuous subcutaneous insulin infusion versus multiple daily injections in adolescents with type I diabetes mellitus: A randomized open crossover trial. *Journal of Pediatric Endocrinology & Metabolism* 2003;16(7):1047-50.	Included in the best quality SR[31]
Davis et al. The initiation of intensive pump therapy at diagnosis of type 1 diabetes mellitus in adolescents: a randomised trial. *Diabetes* 2007;56(Suppl 1):A53.	Only abstract available
Deiss et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care* 2006;29(12):2730-32. (Referenced by Medtronic)	Did not compare IPT with MDI, compared different blood glucose monitoring systems
DeVries et al. A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. *Diabetes Care* 2002;25(11):2074-80.	Included in another SR[34]
Di Bartolo et al. Aspart and lispro insulin, is there any difference when used with an insulin pump treatment? *Diabetes Research and Clinical Practice* 2006;74(Suppl 2):S119-21.	Did not compare IPT with MDI
DiMeglio et al. A randomized, controlled study of insulin pump therapy in diabetic preschoolers. *Journal of Pediatrics* 2004;145(3):380-4.	Included in the best quality SR[31]
Doyle et al. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 2004;27(7):1554-8.	Included in the best quality SR[31]

Fox et al. A randomized controlled trial of insulin pump therapy in young children with type 1 diabetes. *Diabetes Care* 2005;28(6):1277-81.	Included in the best quality SR[31]
Garcia-Garcia et al. Long-term use of continuous subcutaneous insulin infusion compared with multiple daily injections of glargine in pediatric patients. *Journal of Pediatric Endocrinology* 2007;20(1):37-40.	Not an RCT
Garg et al. Glycemic parameters with multiple daily injections using insulin glargine versus insulin pump. *Diabetes Technology & Therapeutics* 2004;6(1):9-15.	Not an RCT
Hanaire-Broutin et al. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. *Diabetes Care* 2000;23(9):1232-5.	Included in another SR[34]
Heinemann et al. Multiple daily SMBG is strongly associated with optimal glucose control in CSII patients. *Diabetes* 2007;56(Suppl 1):A23.	Only abstract available
Heptulla et al. Twenty-four-hour simultaneous subcutaneous Basal-bolus administration of insulin and amylin in adolescents with type 1 diabetes decreases postprandial hyperglycemia. *Journal of Clinical Endocrinology & Metabolism* 2009;94(5):1608-11.	Did not compare IPT with MDI
Hirsch et al. Continuous subcutaneous insulin infusion (CSII)of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. *Diabetes Care* 2005;28(3):533-8.	Included in the best quality SR[31]
Hoogma et al. Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial. *Diabetic Medicine* 2006;23(2):141-7.	Included in the best quality SR[31]
Hoogma et al. Quality of life and metabolic control in patients with diabetes mellitus type 1 treated by continuous subcutaneous insulin infusion or multiple daily insulin injections. *Netherlands Journal of Medicine* 2004;62(10):383-7.	Not an RCT
Kleefstra et al. Marked improvement of quality of life and treatment satisfaction with intraperitoneal insulin (CIPII) compared to CSII in type 1 diabetes. *Diabetologia* 2008;51(Suppl 1):S450-1.	Only abstract available
Kordonouri et al. Age-specific advantages of continuous subcutaneous insulin infusion as compared with multiple daily injections in pediatric patients: one-year follow-up comparison by matched-pair analysis. *Diabetes Care* 2006;28(2):133-4.	Not an RCT
Myneni et al. Comparison of insulin infusion pumps versus basal/bolus insulin injections for treatment of type 1 diabetes mellitus in clinical practice. *Journal of Diabetes Science & Technology* 2009;3(2):403-4.	Only abstract available
Opiari-Arrigan et al. Continuous subcutaneous insulin infusion benefits quality of life in preschool-age children with type 1 diabetes mellitus. *Pediatric Diabetes* 2007;8(6):377-83.	Included in the best quality SR[31]
Pozzilli et al. A 2-year pilot trial of continuous subcutaneous insulin infusion versus intensive insulin therapy in patients with newly diagnosed type 1 diabetes (IMDIAB 8). *Diabetes Technology & Therapeutics* 2003;5(6):965-74.	Included in the best quality SR[31]
Rabbone et al. Intensive insulin therapy in preschool-aged diabetic children: from multiple daily injections to continuous subcutaneous insulin infusion through indwelling catheters. *Journal of Endocrinological Investigation* 2008;31(3):193-5.	Not focused on insulin pump
Schiaffini et al. Basal insulin supplementation in type 1 diabetic children: a long-term comparative observational study between continuous subcutaneous insulin infusion and glargine insulin. *Journal of Endocrinological Investigation* 2007;30(7):572-77.	Not an RCT (contacted author to confirm this)
Simon et al. A comparison of glycaemic variability in CSII vs. MDI treated type 1 diabetic patients using CGMS. *International Journal of Clinical Practice* 2008;62(12):1858-63.	Not an RCT

Tsui et al. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. *Diabetes Care* 2001;24(10):1722-7.	Included in another SR[34]
Weintrob et al. Glycemic patterns detected by continuous subcutaneous glucose sensing in children and adolescents with type 1 diabetes mellitus treated by multiple daily injections vs. continuous subcutaneous insulin infusion. *Archives of Pediatrics & Adolescent Medicine* 2004;158(7):677-84.	Included in the best quality SR[31]
Weintrob et al. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: A randomized open crossover trial. *Pediatrics* 2003;12(3):559-64.	Included in the best quality SR[31]
Weinzimer et al. Prolonged use of continuous glucose monitors in children with type 1 diabetes on continuous subcutaneous insulin infusion or intensive multiple-daily injection therapy. *Pediatric Diabetes* 2009;10(2):91-6.	Not an RCT
Wilson et al. A two-center randomized controlled feasibility trial of insulin pump therapy in young children with diabetes. *Diabetes Care* 2005;28(1):15-19.	Included in the best quality SR[31]
Yates et al. Continuous glucose monitoring-guided insulin adjustment in children and adolescents on near-physiological insulin regimens: a randomized controlled trial. *Diabetes Care* 2006;29(7):1512-17.	Did not compare IPT with MDI

Abbreviations: RCT: randomized controlled trial; SR: systematic review

Appendix T.C: Methodological quality assessment

I. Systematic review quality assessment checklist

(Adapted from various sources[a-d]) (Updated on 29 June 2009)

This checklist contains six quality subsections (grey sections) that, according to the literature, reflect aspects considered essential for a good quality systematic review. If desired, the researcher can use the scores obtained for these six subsections to categorize the review as good, average, or poor quality according to the number of criteria met. This additional categorization is optional. The rating system is flexible in that other criteria can be substituted for some or all of the six criteria in accordance with the priorities and opinions of the assessors.

Study Question

The research question should be established a priori.

Reported: The objectives of the review are clearly stated in the abstract, introduction, or methods.

Partially reported: The objectives of the review are stated in:

- the abstract, introduction, or methods but are vague or unclear; or
- a section of the report other than the abstract, introduction, or methods.

Not reported: The objectives are not stated in any section of the review.

Inclusion and Exclusion Criteria

The participants, interventions, outcome measures, and types of studies considered for analysis should be established a priori.

Reported: All four elements (participants, interventions, outcome measures, types of studies) are reported in the abstract, introduction, or methods section of the review.

Partially reported: Only three of the four elements are reported in the abstract, introduction, or methods section.

Not reported:

- Less than three of the four elements are reported in the abstract, introduction, or methods section; or
- The first mention of any of these elements occurs in the results section.

Search Strategy

Electronic databases

Reported: At least one electronic database was searched, and the names of the databases are provided.

Partially reported: At least one electronic database was searched, but the names are not provided.

Not reported: Electronic databases were not searched or are not mentioned in the review.

Quality subsection 1: At least MEDLINE and one other relevant literature database

Yes: MEDLINE and one other relevant literature database were searched.

Unclear: It was unclear whether MEDLINE and one other relevant literature database were searched because a complete list of all the electronic databases searched is not provided.

No:

- the review stated that neither MEDLINE nor another relevant literature database was searched,
- neither MEDLINE nor another relevant literature database is mentioned in the complete list of electronic databases searched, or
- only one of the two the databases (MEDLINE or one other relevant database) was searched.

Other sources

Reported: At least one additional resource or method, other than searching electronic databases, was used to identify relevant literature (e.g., pearling, or review of reference lists in retrieved articles, handsearching of journals).

Partially reported: Other resource or methods were used, but details are not provided.

Not reported: The review did not use other resource or methods to identify relevant literature or does not mention it.

Data Extraction

Data extraction method

Reported: The data extraction process is described.

Partially reported: A data extraction process is mentioned, but no details are provided.

Not reported: A data extraction process was not used or described.

Quality subsection 2: Standardized method

Yes: The data categories extracted are listed, or the use of a standardized data extraction form is mentioned.

Unclear: The review states that a standardized data extraction process was used but does not list the data categories extracted or mention the use of a standardized data extraction form.

No: The data categories extracted are not listed, or the use of a standardized data extraction form is not mentioned.

Quality subsection 3: Independent data extraction by at least two reviewers

Yes: Data were extracted independently by at least two reviewers.

Unclear: The number of reviewers who extracted data is not stated.

No: Details of data extraction were not provided or data were extracted by

- only one reviewer or
- one reviewer and checked by another.

Quality Assessment

Criteria used to assess the validity of included studies

Reported: A quality assessment tool or checklist was used, and details are provided (e.g., name or source).

Partially reported: A quality assessment tool or checklist was used, but no details are provided.

Not reported::

- a quality assessment tool or checklist was not used or mentioned or
- studies were categorized only according to a level of evidence hierarchy.

Quality subsection 4:
Independent quality assessment by at least two reviewers

Yes: The quality of the included studies was assessed independently by at least two reviewers.

Unclear: The number of reviewers who appraised study quality is not stated.

No: Studies were assessed by:

- only one reviewer or
- one reviewer and checked by another.

Interrater agreement

Reported: The review mentions that a consensus method was used or provides a statement of the degree of difference/equivalence between the reviewers or a statistical measure of interrater agreement.

Partially reported: The review mentions that interrater agreement was measured but does not provide a statement of the degree of difference or equivalence or a statistical measure of interrater agreement.

Not reported: The review does not provide any information on interrater agreement.

Data Analysis/Synthesis

Only **one** of the three methods for data analysis or synthesis can be assessed. Select the data analysis type according to the definitions below. Score only the quality subsection that pertains to the particular data analysis method used in the review.

Qualitative review:

A narrative summary of the study results with no statistical analysis or pooling of results.

Quality subsection 5a:
Study quality used in analysis or discussion of study results

Yes: Results of the included studies are discussed or analyzed in terms of their quality.

Unclear:

- Study quality was assessed but is either not used at all or is only used to analyze some of the included studies.
- The review mentions selective inclusion of 'quality' studies, but without further assessment of their quality (e.g. only RCTs were included but the robustness of their execution was not assessed).

No:

- The results of the included studies are not discussed or analyzed in terms of their quality.
- Study quality was not assessed.

Semi-quantitative review:

Incorporates a statistical analysis of individual studies without pooling the results (e.g., relative risks calculated for individual study outcomes) or pooling of results using only descriptive statistics (e.g., median, mean, mode, frequency).

Quality subsection 5b: Confidence interval and measures of dispersion reported

Yes: Confidence intervals or measures of dispersion (range, standard deviation, standard error of the mean) are reported for all relevant analyses.

Unclear:

- Confidence intervals or measures of dispersion are only reported for some of the relevant analyses.
- Confidence intervals are reported for all relevant analyses, but the level of confidence is not specified (e.g., unclear if 95% or 99% confidence intervals were calculated).
- Measures of dispersion are reported for all relevant analyses, but the type is not specified (e.g. standard deviation or standard error).

No: Confidence intervals or measures of dispersion are not reported.

Meta-analysis:

A pooled effect estimate is calculated for at least two studies. Reviews that contain a meta-analysis of some studies and a qualitative analysis of the remaining studies are considered a 'meta-analysis'.

Quality subsection 5c: Precision of results reported

Yes: Confidence intervals are reported for all pooled effect estimates.

Unclear:

- Confidence intervals are reported for some but not all pooled effect estimates.
- Confidence intervals are reported for all pooled effect estimates, but the level of confidence is not specified (e.g., unclear if 95% or 99% confidence intervals were calculated).

No: Confidence intervals are not reported.

Quality subsection 5d: Test of study heterogeneity conducted

Yes: A statistical analysis of study heterogeneity is reported for all pooled studies.

Unclear:

- A statistical analysis of study heterogeneity is reported for some but not all pooled studies.
- Heterogeneity was examined visually or a statistical analysis of study heterogeneity is reported for all pooled studies, but the type of model used is not specified (e.g. fixed-effect or random-effects).

No: A statistical analysis of study heterogeneity was not conducted.

Test for publication bias

Reported: Publication bias was analyzed or a reason was provided for why it was not.

Partially reported:

- The review mentions analyzing publication bias but does not present the results.
- The review states that publication bias was not analyzed but does not explain why.

Not reported: There was no mention of analyzing publication bias.

Concluding Section

Potential methodological limitations

Reported: The methodological limitations or advantages of the review are described in a separate section or paragraph.

Partially reported: The description of the methodological limitations or advantages of the review is cursory (e.g., single sentence or no separate paragraph or section).

Not reported: There is no mention of the potential methodological limitations or advantages of the review.

Clinical application of results

The clinical application of results is considered adequate if all of the following four elements are present in the concluding section (includes discussion) or statement of the review: treatment, treatment effect, patient group, and comparator.

Reported: All four elements are present.

Partially reported: Only three of the four elements are present.

Not reported: Less than three of the four elements are present.

Incorporation of methodological quality

The review should take into account the methodological quality of the included studies when formulating the conclusions.

Reported: The methodological quality of the included studies is mentioned in the concluding section (includes discussion) or statement of the review.

Partially reported: The study types, as designated by a level of evidence hierarchy category, are mentioned in the concluding section (includes discussion) or statement of the review, but not the quality of the studies.

Not reported: The methodological quality of the included studies is not mentioned in the concluding section (includes discussion) or statement of the review.

Quality subsection 6: Conclusions supported by results

Yes: The conclusions drawn by the authors of the review are supported by the evidence presented in the results section.

Unclear: Some, but not all, of the conclusions drawn by the authors of the review are supported by the evidence presented in the results section.

No: The conclusions drawn by the authors of the review are not supported by the evidence presented in the results section.

Conflict of interest and funding

Conflict of interest

Reported: A statement of conflict of interest (if any) is provided.

Partially reported: A conflict of interest is mentioned, but details are not provided.

Not reported: A statement of conflict of interest (if any) is not provided.

Sources of funding

Reported:

- funding sources are mentioned or
- the review was developed without external funding (e.g., authors were employed by a university or volunteered time to produce a Cochrane Review).

Partially reported: External funding is mentioned, but details are not provided.

Not reported: Funding sources are not mentioned.

Optional Quality Rating System

The quality of systematic reviews can be assessed according to how well their methods exclude bias and confounding by examining the search strategy used; how the data extraction, quality assessment of the included studies, and data analysis or synthesis were conducted; and whether the conclusions of the review match the results. Thus, the quality of the review can be rated numerically with respect to the six quality subsections (grey boxes above) as follows.

Good – six criteria met, or five criteria met and one criterion 'unclear'.

Average – one criterion not met, or one criterion not met and one criterion 'unclear', or two criteria 'unclear'.

Poor – at least two criteria not met.

N.B. For a criterion to have been 'met', it must be scored as 'yes' (✓). For meta-analyses, the two applicable quality subsections (5c and 5d) are counted as a single quality criterion. Therefore, to meet the fifth quality criterion for meta-analyses, both 5c and 5d must be scored as 'yes' (✓).

References

a. Fishbain D, Cutler RB, Rosomoff HL, Rosomoff RS. What is the quality of the implemented meta-analytic procedures in chronic pain treatment meta-analyses? *Clinical Journal of Pain* 2000;16(1):73-85.

b. Aggressive Research Intelligence Facility, University of Birmingham. ARIF Critical Appraisal Checklist. [cited 2002 Feb 19]. Available from: *http://www.bham.ac.uk/arif/ca.process.htm*.

c. University of Alberta. Evidence Based Medicine Tool Kit. Edmonton, AB: University of Alberta. [cited 2000 Nov 1]. Available from: *http://www.med.ualberta.ca/ebm/main.htm*.

d. Greenhalgh T. How to read a paper: papers that summarise other papers (systematic reviews and meta-analysis). *BMJ* 1997;315:672-5.

Table T.C.1: Results of quality assessment for systematic reviews

Criteria		Fatourechi[31]	Monami[34]	Pickup[35]	Jeitler[36]
Study question established a priori		●	●	●	●
Inclusion/exclusion criteria		●	●	●	●
Search strategy	Electronic databases	●	●	●	●
	1. At least MEDLINE and one other relevant database	✓	×	✓	✓
	Other sources	●	○	●	●
Data extraction	Data extraction method	●	◐	●	◐
	2. Standardized method	✓	×	?	×
	3. Independent data extraction by at least two reviewers	✓	✓	✓	✓
Quality assessment	Criteria used to assess the validity of included studies	●	●	◐	●
	4. Independent quality assessment by at least two reviewers	✓	?	?	?
	Interrater agreement for quality assessment	●	○	○	○
Data analysis/synthesis	Qualitative review	N/A	N/A	N/A	N/A
	5a. Study quality used in analysis or discussion of study results	N/A	N/A	N/A	N/A
	Semi-quantitative review	N/A	N/A	N/A	N/A
	5b. Confidence intervals or measures of dispersion reported	N/A	N/A	N/A	N/A
	Meta-analysis	●	●	●	●
	5c. Precision of results reported	✓	✓	✓	✓
	5d. Test of heterogeneity conducted	✓	×	✓	✓
Test for publication bias		●	○	●	○
Concluding section	Potential methodological limitations/advantages	●	○	●	●
	Clinical application of results	●	●	●	●
	Incorporation of methodological quality	●	○	◐	●
	6. Conclusions supported by results	✓	✓	✓	✓
Conflict/ funding	Conflict of interest (if any)	●	●	●	●
	Sources of funding	○	●	●	●
Quality rating	Six criteria in grey areas	6/6 good	2.5/6 poor	4/6 average	4/6 average

Symbols and abbreviations: full: ●; not at all; ○; partial: ◐; yes: ✓; no = ×; not available: NA

Table T.C.1: Results of quality assessment for systematic reviews (cont'd)

Criteria		Churchill[37]	Pankowska[38]	Farrar[32]	Mukhopadhyay[39]
Study question established a priori		●	●	●	●
Inclusion/exclusion criteria		●	●	●	●
Search strategy	Electronic databases	●	●	●	●
	1. At least MEDLINE and one other relevant database	✓	✓	✓	✓
	Other sources	○	●	●	●
Data extraction	Data extraction method	○	●	◐	○
	2. Standardized method	×	?	×	×
	3. Independent data extraction by at least two reviewers	?	✓	✓	?
Quality assessment	Criteria used to assess the validity of included studies	●	●	●	●
	4. Independent quality assessment by at least two reviewers	✓	✓	✓	✓
	Interrater agreement for quality assessment	○	○	○	○
Data analysis/synthesis	Qualitative review	●	N/A	N/A	N/A
	5a. Study quality used in analysis or discussion of study results	✓	N/A	N/A	N/A
	Semiquantitative review	N/A	N/A	N/A	N/A
	5b. Confidence intervals or measures of dispersion reported	N/A	N/A	N/A	N/A
	Meta-analysis	N/A	●	●	●
	5c. Precision of results reported	N/A	✓	✓	✓
	5d. Test of homogeneity conducted	N/A	✓	✓	✓
Test for publication bias		○	●	○	●
Concluding section	Potential methodological limitations/advantages	○	○	○	●
	Clinical application of results	●	●	○	●
	Incorporation of methodological quality	●	●	●	●
	6. Conclusions supported by results	✓	✓	✓	✓
Conflict/ funding	Conflict of interest (if any)	○	○	●	○
	Sources of funding	○	○	○	○
Quality rating	Six criteria in grey areas	4/6 average	5/6 good	5/6 average	4/6 average

Table T.C.2: Results of quality assessment for HTAs

Criteria		Medical Advisory Secretariat 2009[40]	Campbell et al. 2008[41]
Study question established a priori		●	●
Inclusion/exclusion criteria		●	●
Search strategy	Electronic databases	●	●
	1. At least MEDLINE and one other relevant database	✓	✓
	Other sources	●	●
Data extraction	Data extraction method	○	●
	2. Standardized method	×	✓
	3. Independent data extraction by at least two reviewers	?	×
Quality assessment	Criteria used to assess the validity of included studies	●	●
	4. Independent quality assessment by at least two reviewers	?	×
	Inter-rater agreement for quality assessment	○	N/A
Data analysis/synthesis	Qualitative review	●	N/A
	5a. Study quality used in analysis or discussion of study results	✓	N/A
	Semi-quantitative review	N/A	N/A
	5b. Confidence intervals or measures of dispersion reported	N/A	N/A
	Meta-analysis	N/A	●
	5c. Precision of results reported	N/A	✓
	5d. Test of homogeneity conducted	N/A	✓
Test for publication bias		○	○
Concluding section	Potential methodological limitations/advantages	○	●
	Clinical application of results	●	●
	Incorporation of methodological quality	●	●
	6. Conclusions supported by results	✓	✓
Conflict/ funding	Conflict of interest (if any)	●	○
	Sources of funding	N/A	●
Quality rating	Six criteria in grey areas	3/6 poor	4/6 poor

Symbols and abbreviations: full: ●; not at all; ○; partial: ◐; yes: ✓; no = ×; not available: NA

II. Quality assessment tool for randomized controlled trials[33]

Table T.C.3-1: The Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgment
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of or during enrolment.	Was allocation adequately concealed?
Blinding of outcome assessors *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition or exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions or entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Table T.C.3-2: Criteria for judging risk of bias in the 'Risk of bias' assessment tool

Sequence generation Was the allocation sequence adequately generated? [Short form: *Adequate sequence generation*?]	
Criteria for a judgment of **yes** (i.e., low risk of bias)	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table • Using a computer random number generator • Coin tossing • Shuffling cards or envelopes • Throwing dice • Drawing of lots • Minimization* *Minimization may be implemented without a random element, and this is considered equivalent to being random.
Criteria for the judgment of **no** (i.e., high risk of bias)	The investigators describe a nonrandom component in the sequence generation process. Usually, the description would involve some systematic, nonrandom approach, for example: • Sequence generated by odd or even date of birth • Sequence generated by some rule based on date (or day) of admission • Sequence generated by some rule based on hospital or clinic record number Other nonrandom approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious; they usually involve judgment or some method of nonrandom categorization of participants, for example: • Allocation by judgment of the clinician • Allocation by preference of the participant • Allocation based on the results of a laboratory test or a series of tests • Allocation by availability of the intervention
Criteria for the judgment of **unclear** (uncertain risk of bias)	Insufficient information about the sequence generation process to permit judgment of **yes** or **no**.
Allocation concealment Was allocation adequately concealed? [Short form: *Allocation concealment*?]	
Criteria for a judgment of **yes** (i.e., low risk of bias)	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based, and pharmacy-controlled, randomization)

	• Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes
Criteria for the judgment of **no** (i.e., high risk of bias)	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on the following: • Using an open random allocation schedule (e.g., a list of random numbers) • Assignment envelopes were used without appropriate safeguards (e.g., if envelopes were unsealed or non-opaque or not sequentially numbered) • Alternation or rotation • Date of birth • Case record number • Any other explicitly unconcealed procedure
Criteria for the judgment of **unclear** (uncertain risk of bias)	Insufficient information to permit judgment of **yes** or **no**. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment; for example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque, and sealed.
Blinding of outcome assessors Was knowledge of the allocated interventions adequately prevented during the study? [Short form: *Blinding*?]	
Criteria for a judgment of **yes** (i.e., low risk of bias).	Any one of the following: • No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding • Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the nonblinding of others unlikely to introduce bias
Criteria for the judgment of **no** (i.e., high risk of bias)	Any one of the following: • No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding • Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias
Criteria for the judgment of **unclear** (uncertain risk of bias)	Any one of the following: • Insufficient information to permit judgment of **yes** or **no** • The study did not address this outcome

Incomplete outcome data Were incomplete outcome data adequately addressed? [Short form: *Incomplete outcome data addressed?*]	
Criteria for a judgment of **yes** (i.e., low risk of bias)	Any one of the following: • No missing outcome data • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias) • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size • Missing data have been imputed using appropriate methods
Criteria for the judgment of **no** (i.e., high risk of bias)	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization • Potentially inappropriate application of simple imputation
Criteria for the judgment of **unclear** (uncertain risk of bias)	Any one of the following: • Insufficient reporting of attrition, exclusions to permit judgment of **yes** or **no** (e.g., number randomized not stated, no reasons for missing data provided) • The study did not address this outcome

Selective outcome reporting Are reports of the study free of suggestion of selective outcome reporting? [Short form: *Free of selective reporting*?]	
Criteria for a judgment of **yes** (i.e., low risk of bias)	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Criteria for the judgment of **no** (i.e., high risk of bias)	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported • One or more primary outcomes is reported using measurements, analysis methods, or subsets of the data (e.g., subscales) that were not pre-specified • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect) • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis • The study report fails to include results for a key outcome that would be expected to have been reported for such a study
Criteria for the judgment of **unclear** (uncertain risk of bias).	Insufficient information to permit judgment of **yes** or **no**. It is likely that the majority of studies will fall into this category.
Other potential threats to validity Was the study apparently free of other problems that could put it at a risk of bias? [Short form: *Free of other bias*?]	
Criteria for a judgment of **yes** (i.e., low risk of bias)	The study appears to be free of other sources of bias.
Criteria for the judgment of **no** (i.e., high risk of bias)	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Stopped early due to some data-dependent process (including a formal-stopping rule); or • Had extreme baseline imbalance; or • Has been claimed to have been fraudulent; or • Had some other problem.

Criteria for the judgment of **unclear** (uncertain risk of bias)	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.

Table T.C.3-3: Possible approach for *summary assessments* outcome (across domains) within and across studies

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains	Most information is from studies at low risk of bias
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains	Most information is from studies at low or unclear risk of bias
High risk of bias	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results

Table T.C.3-4: Results of quality assessment for randomized controlled trials

Criteria	Bolli et al. 2009[42]	Peyrot & Rubin 2009[6]	Thomas et al. 2007[28]	Nabhan et al. 2009[43]	Nuboer et al. 2008[44]	Skogsberg et al. 2008[22]
Sequence generation Was the allocation sequence adequately generated?	?	?	?	?	?	?
Allocation concealment Was allocation adequately concealed?	✓	?	?	?	✓	?
Blinding of outcome assessors Was knowledge of the allocated intervention adequately prevented during the study?	?	?	?	?	?	?
Incomplete outcome data Were incomplete outcome data adequately addressed?	?	?	?	×	×	×
Selective outcome reporting Are reports of the study free of suggestion of selective outcome reporting?	✓	?	✓	✓	✓	✓
Other sources of bias Was the study apparently free of other problems that could put it at a high risk of bias?	✓	×	✓	×	×	×
Summary **Risk of bias within the study**	Unclear	Unclear	Unclear	Unclear-high	Unclear-high	Unclear-high

Symbols: yes: ✓; no: ×; unclear: ?

Appendix T.D: Evidence from systematic reviews/HTAs and new RCTs (Evidence table)

Abbreviations for Appendix T.D:

A1C – glycosylated hemoglobin

BG – blood glucose

BMI – body mass index

CGM – continuous glucose monitoring

CI – confidence interval

CSII – continuous subcutaneous insulin infusion

DKA – diabetes ketoacidosis

DM – diabetes mellitus

EOS – end of study

F – female

FU – follow-up

IPT – insulin pump therapy

M – male

MA – meta-analysis

MDI – multiple daily injection

NA – not available

NPH – neutral protamine Hagedorn

NR – not reported

QA – quality assessment

QoL – quality of life

RCTs – randomized controlled trials

RT – real time

SMBG – self-monitoring of blood glucose

SH – severe hypoglycemia

SR – systematic review

T1DM – type 1 diabetes

TDD – total daily dose

TEAE – treatment-emergent adverse event

U – unit

WMD – weighted mean difference

Note*:* In Table T.D.1, A1C values are presented in weighted mean difference (WMD) with 95% confidence interval (95% CI) unless otherwise indicated; negative values of A1C indicate that treatment effects favour IPT

Table T.D.1: Summary of the included systematic reviews

Study	Study selection	Included studies	Results/conclusion
Fatourechi et al. 2009[31] Meta-analysis **Objective** To summarize evidence on the effect of IPT and MDI on glycemic control and hypoglycemia **Search** ***Database searched:*** MEDLINE, EMBASE, Cochrane's CENTRAL (2002 to 17 March 2008) ***Other source:*** reference list of included trials, unpublished and ongoing trials, contacted pump manufacturers	**Inclusion criteria** ***Study design:*** RCTs published between 2002 and March 2008 ***Population:*** adults or children with diabetes of any kind ***Intervention:*** IPT vs. MDI ***Outcome measures:*** glycemic control and hypoglycemia **Exclusion criteria** Critical illness or pregnancy	**Study characteristics** ***No. of included RCTs:*** 13 Adults: 5 RCTs Preschool children: 4 RCTs Children and adolescents: 4 RCTs ***No. of included patients:*** 667 Adults: 467 Preschool children: 106 Children and adolescents: 94 ***Duration of DM*** *(yr):* Adults: mean 8 to 25 Preschool children: mean 1 to 1.8 Children and adolescents: mean < 1 month to 6.2 yrs ***Inclusion of patients with previous SH:*** 3 RCTs excluded and 1 RCT included patients with previous SH ***Duration of follow-up*** *(month):* 1.2 to 12.1 **Study quality** ***QA criteria:*** 1) allocation concealment, 2) blinding of outcome assessors, 3) loss to follow-up; in addition, funding source ***QA results:*** The studies implemented adequate allocation concealment; outcome assessors were generally aware of the treatment arm. Loss to follow-up was substantial (range 0 to 25%, median 8.5%); 11 trials received material or financial support from manufacturers.	**Safety** ***DKA:*** NA ***SH:*** no ss difference between the two groups ***Site infection:*** NA ***Pump malfunction:*** NA **Efficacy** ***A1C*** *(%):* compared to MDI, IPT reduced A1C by 0.2% (0.1 to 0.3) in all patients, as well as in children and adult patients Pooled WMD (95% CI): All groups: −0.18 (−0.27 to −0.09)(ss) Adults: −0.19 (−0.27 to −0.11)(ss) Children: −0.20 (−0.43 to −0.03)(ss) ***Patient satisfaction*****:** NA ***QoL:*** NA ***Secondary complications of DM:*** NA **Conclusion:** Contemporary evidence indicates that compared to MDI, IPT slightly reduced A1C in adults with T1DM, with unclear impact on hypoglycemia.

Table T.D.1: Summary of the included systematic reviews (cont'd)

Study	Study selection	Included studies	Results/conclusion
Monami et al. 2009[34] Meta-analysis **Objective** To assess differences in efficacy and hypoglycemic risk between IPT using short-acting analogues and MDI in patients with T1DM **Search** ***Database searched:*** MEDLINE (through 10 July 2008) ***Other source:*** NA	**Inclusion criteria** ***Study design:*** RCTs with a duration ≥ 12 weeks ***Population:*** T1DM ***Intervention:*** IPT vs. MDI using short-acting analogs ***Outcome measures:*** hypoglycemia, A1C **Exclusion criteria** RCTs with study duration < 12 weeks	**Study characteristics** ***No. of included RCTs:*** 11 Adults: 6 RCTs Preschool children: 4 RCTs Children and adolescents: 1 RCT ***No. of included patients:*** 883 Adults: 753 Preschool children: 98 Children/adolescents: 32 ***Duration of DM*** *(yr):* 1 to 25 ***Inclusion of patients with previous SH:*** NA ***Duration of follow-up*** *(months):* Adults: 3.7 to 8.4 Preschool children: 6.1 to 12.1 Children and adolescents: 3.7 **Study quality** ***QA criteria:*** 1) adequate description of randomization, 2) allocation, 3) blinding, 4) dropout procedure ***QA results:*** All studies had adequate reporting of dropout; six studies had adequate reporting of randomization and allocation.	**Safety** ***DKA:*** NA ***SH:*** 16 patients in IPT vs. 21 patients in MDI experienced at least 1 SH episode (nss) ***Site infection:*** NA ***Pump malfunction:*** NA **Efficacy** ***A1C*** *(%):* significantly reduced in IPT with either lispro: −0.2 (−0.4 to −0.1; P = 0.001) or aspart: −0.6 (−1.0 to −0.2; P = 0.002) For patients with mean age > 10 years: significant lower in IPT group: −0.3 (−0.4 to −0.2; P < 0.001) For younger patients: no significant difference −0.1 (−0.5 to 0.3; P = 0.48) ***Patient satisfaction:*** NA ***QoL:*** NA ***Secondary complications of DM:*** NA **Conclusion:** IPT using short-acting insulin analogues can improve metabolic control in patients with T1DM who are unable to reach glycemic targets with conventional basal-bolus regimens with MDI.

Table T.D.1: Summary of the included systematic reviews (cont'd)

Study	Study selection	Included studies	Results/conclusion
Pickup & Sutton 2008[35] Meta-analysis **Objective:** To conduct a meta-analysis comparing severe hypoglycemia and glycemic control during IPT and MDI in patients with T1DM **Search** ***Database searched:*** MEDLINE (1996 to 2005), EMBASE (1996 to 2006) ***Other source:*** reference list of the retrieved articles	**Inclusion criteria** ***Study design:*** RCTs or before/after studies in which patients switched from MDI to IPT and acted as their own control, published no earlier than 1996 ***Population:*** T1DM of ≥ 6 months duration of IPT, where the rate of SH during MDI > 10 episodes/100 patient years of treatment ***Intervention:*** IPT vs. MDI ***Outcome measures:*** SH, A1C **Exclusion criteria** ***Study design:*** studies with two nonrandomized groups who had chosen to be on either therapy ***Population***: T2DM, newly diagnosed T1DM, pregnancy	**Study characteristics** ***No. of included RCTs:*** six (three on patients with high rate of SH during MDI) Adults: four RCTs Children and adolescents: two RCTs ***No. of included patients:*** 402 ***Duration of DM*** *(yr):* 2 to 21.8 ***Inclusion of patients with previous SH:*** 39 to 61 SH episodes/100 patient years of MDI treatment ***Duration of follow-up*** *(month):* 1.25 to 7 **Study quality** ***QA criteria:*** 1) trial design; 2) loss to follow-up or discontinuation rate; 3) blinding of assessment of the main outcome (hypoglycemia); 4) description of method of randomization and allocation concealment (for RCTs) ***QA results:*** No studies clearly reported that there was blinding of severe hypoglycemia rate assessment, and one RCT reported satisfactory concealment of allocation and a description of the method of randomization.	**Safety** ***DKA:*** NA ***Hypoglycemia:*** markedly reduced during IPT compared with MDI, with a rate ratio of 2.89 (95% CI 1.45 to 5.76) ***Infection:*** NA ***Pump malfunction:*** NA **Efficacy** ***A1C*** *(%):* better control with IPT compared to MDI, A1C difference −0.21% (−0.13 to −0.30%) ***Patient satisfaction:*** NA ***QoL:*** NA ***Secondary complications of DM:*** NA **Conclusion**: IPT produces a significant and substantial reduction in SH in T1DM compared with non-analogue-based MDI. The accompanying lowering in A1C is greatest in the most poorly controlled patients. (**Note:** this conclusion was based on the results of RCTS and before/after studies.)

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Table T.D.1: Summary of the included systematic reviews (cont'd)

Study	Study selection	Included studies	Results/conclusion
Jeitler et al. 2008[36] Meta-analysis **Objective** To compare the effects of IPT with those of MDI on glycemic control, risk of hypoglycemic episodes, insulin requirements, and adverse events in patients with type 1 and type 2 diabetes **Search** ***Database searched:*** MEDLINE, EMBASE, CENTRAL up to March 2007 for RCTs ***Other source:*** Cochrane library, DARE, HTA Database, NHSEED for secondary literature, and handsearch of reference lists from relevant secondary literature	**Inclusion criteria** ***Study design:*** RCTs ***Population:*** T1DM or T2DM, any age, ≥ 10 patients ***Intervention:*** treatment ≥ 4 weeks, same type of insulin used in both treatment groups ***Outcome measures:*** glycemic control (A1C), insulin requirement, severe or mild hypoglycemia episode, adverse events **Exclusion criteria** Pregnant women, IPT used night only, studies on mixed group (T1DM, T2DM, children) without separate reporting	**Study characteristics** ***No. of included RCTs:*** 20 (31 publications) Adults: 17 RCTs (27 publications) Preschool children: 1 RCT Children and adolescents: 2 RCTs (three publications) ***No. of included patients:*** 982 Adults: 908 Preschool children: 22 Children and adolescents: 52 ***Duration of DM*** *(yr):* NA ***Inclusion of patients with previous SH:*** NA ***Duration of follow-up*** *(months):* Adults: 1.2 to 24 Preschool children: 3.7 in both trials Children/adolescents: 12 **Study quality** ***QA criteria:*** 11 criteria based on Cochrane handbook,[55] Jadad,[56] and Schulz scale[57] Scoring system: A. plausible bias is unlikely to affect the results seriously; B. plausible bias raises some doubt about the results; C. plausible bias seriously weakens confidence in the results ***QA results:*** Of 17 RCTs on adults, 2 scored B and 15 scored C. Of 3 RCTs on children, 2 scored B and 1 scored C.	**Safety** ***DKA:*** Adults: inconsistent results; two RCTs published since 2004: 1 in IPT vs. 0 in MDI, 4 in IPT vs. 0 in MDI Preschool children: none Children and adolescents: one study reported one DKA in each group ***SH:*** Adults: overall, SH was rare. Proportion of patients with SH ranged from 0 to 0.13 in the IPT group and from 0 to 0.4 in the MDI group. Preschool children: in one study, 1 in IPT vs. 4 in MDI; in the other study, 1 in each group. Children and adolescents: 1 in each group ***Site infection:*** one RCT reported three episodes in one adult patient treated with IPT. ***Pump malfunction:*** four RCTs on adults reported infusion problems with IPT. ***Other:*** only one reported death (in a 1988 study). **Efficacy** ***A1C*** *(%)*: Adults (6 RCTs): significantly reduced in patients with IPT: WMD −0.4 (−0.65 to −0.20)(ss) Preschool children: significantly lower in IPT group Children and adolescents: slightly higher in IPT group (nss) ***Patient satisfaction:*** NA ***QoL:*** NA ***Secondary complications:*** NA **Conclusion:** IPT in adults and adolescents with T1DM resulted in greater reduction of A1C than in adult patients without a higher rate of hypoglycemia.

Table T.D.1: Summary of the included systematic reviews (cont'd)

Study	Study selection	Included studies	Results/conclusion
Churchill et al. 2009[37] **Objective** To evaluate the safety and efficacy of IPT in young children with T1DM **Search** ***Database searched:*** MEDLINE (1996 to March 2008), CINAHL (1996 to March 2008) ***Other source:*** NA	**Inclusion criteria** ***Study design:*** RCTs or quasi-experimental design ***Population:*** preschool children (≤ 6 years) with T1DM ***Intervention:*** IPT vs. MDI ***Outcome measures:*** A1C and hypoglycemia episodes **Exclusion criteria** NA	**Study characteristics** ***No. of included RCTs:*** 7 (3 RCTs, 4 quasi-experimental studies, results from the 3 RCTs are reported below unless indicated otherwise) ***No. of included patients:*** 78 (ranging from 19 to 37) ***Duration of DM*:*** 6 months to 2 years ***Inclusion of patients with previous SH:*** NA ***Duration of follow-up*** *(months):* 6 to 12 **Study quality** ***QA criteria:*** 1) study design, 2) blinding, 3) accounting for withdrawal or dropout, 4) defined outcome measure and documentation of hypoglycemic episodes, 5) method for measuring A1C, 6) defined study objectives, 7) clearly described interventions, 8) intension to treat analysis Total score: 7 ***QA results:*** Two RCTs scored 6 out of 7. One scored 5 out of 7.	**Safety** ***DKA:*** NA ***SH:*** Two RCTs showed a trend of decreasing frequency of hypoglycemia among pump users. One RCT reported no difference in severe symptomatic hypoglycemia between the two groups but a slight, statistically significant increase in meter-detected mild or moderate hypoglycemia in the IPT group at 6 months ***Site infection:*** NA ***Pump malfunction:*** NA ***Other:*** tape allergy (led to discontinuation of IPT) **Efficacy** ***A1C*** *(%):* decreased in all RCTs following IPT; in one RCT: at 3 months: IPT 8.4 ± 0.5 vs. MDI 8.8 ± 0.7 (ss), but nss at 6 months; no differences between the two groups in two RCTs ***Patient satisfaction:*** NA ***QoL:*** two RCTs used different modified versions of DQoL survey and found improvement in parental QoL measures ***Secondary complications of DM:*** NA ***Neuro-cognitive function, child behaviour changes:*** NA **Conclusion:** IPT is a safe and effective method of insulin delivery in young children. When parents are highly motivated, IPT should be offered as a mode of insulin delivery for this age group.

* Based on data from seven studies

Table T.D.1: Summary of the included systematic reviews (cont'd)

Study	Study selection	Included studies	Results/conclusion
Pankowska et al. 2009[38] Meta-analysis **Objective** To investigate potential effects of IPT compared with MDI on glycemic control in children with T1DM **Search** ***Database searched:*** MEDLINE (1966 to January 2007), EMBASE (1980 to January 2007), The Cochrane Database of Systematic Reviews (Issue 4, 2006) and the Cochrane Controlled Trials Register (Issue 4, 2006); search was updated in October 2007 ***Other source:*** reference list from original studies and review articles were identified	**Inclusion criteria** ***Study design:*** parallel RCTs or randomized crossover studies ***Population:*** children, adolescents, and young adults aged 1 to 21 years with T1DM and minimum duration of diabetes of 3 months ***Intervention:*** comparing IPT with MDI with a minimum study duration of 8 weeks ***Outcome measures:*** Primary: glycemic control (A1C) Secondary: total insulin dose, SH rates, DKA rates, therapy discontinuation rate, BMI, QoL, other relevant data **Exclusion criteria** Letters to editors, abstracts, communications from scientific meetings minutes	**Study characteristics** ***No. of included RCTs:*** 6 Preschool children: 3 RCTs Children and adolescents: 3 RCTs ***No. of included patients:*** 165 (81 in IPT vs. 84 in MDI) Preschool children: 87 Children and adolescents: 78 ***Duration of DM*** *(year):* NA ***Inclusion of patients with previous SH:*** NA ***Duration of follow-up*** *(months):* 4 to 12 **Study quality** ***QA criteria:*** 1) allocation concealment, 2) blinding of investigators, 3) participants, 4) outcome assessors and data analysts, 5) comprehensive follow-up ***QA results:*** Only two RCTs used adequate method of generating the randomization scheme. All RCTs were open-label trials. Only two RCTs provided an adequate description of ITT analysis. All trials included an adequate number of participants in the final analysis.	**Safety** ***DKA:*** Preschool children: one RCT reported one episode in IPT vs. 0 in MDI (nss) Children and adolescents: one RCT reported one episode in IPT vs. 0 in MDI (nss) ***SH:*** four RCTs reported less episodes with IPT group than with MDI (nss) ***Site infection:*** NA ***Pump malfunction:*** NA **Efficacy** ***A1C*** *(%):* (5 RCTs, n = 136) significant lower in IPT group compared with MDI group: WMD − 0.24 (− 0.41 to − 0.07; P < 0.001) (no subgroup analysis for different ages) ***Patient satisfaction:*** Children and adolescents: significant higher in IPT group (one study) ***QoL:*** Preschool children: improved in IPT group (one study), no difference in another study Children and adolescents: no difference reported in one study ***Secondary complications of DM:*** NA ***Neuro-cognitive function, child behaviour changes:*** NA **Conclusion:** Five of the six RCTs taken separately did not show any improvement in glycemic control in patients treated with IPT compared with MDI. However, the meta-analysis of RCTs indicates that IPT is more effective than MDI. In a short period of time, IPT does not increase the risk of DKA. The low rates of discontinuation indicate that IPTis preferred by children.

Table T.D.1: Summary of the included systematic reviews (cont'd)

Study	Study selection	Included studies	Results/conclusion
Farrar et al. 2007[32] Cochrane review, meta-analysis **Objective** To conduct a systematic review of randomized controlled trials comparing IPT with MDI of insulin for pregnant women with diabetes **Search** ***Database searched:*** Cochrane Pregnancy and Childbirth Group's Trials Register* (November 2006) ***Other source:*** NA	**Inclusion criteria** ***Study design:*** published or unpublished RCTs ***Population:*** pregnant women with pre-existing and gestational diabetes ***Intervention:*** comparison of IPT vs. MDI ***Outcome measures:*** Main outcomes: peri-natal mortality, fetal anomaly, hypo- and hyperglycemic episodes requiring intervention, admission, and length of stay on special care baby unit due to hypoglycemia Additional outcomes: *For the mother*: diabetic control, rate of antenatal clinic visits and admission for treatment relating to diabetic control, rate of induction of labour, rate of operative delivery, rate of severe perineal trauma, rate of pre-eclampsia, postpartum hemorrhage, abruption, postpartum infection and postnatal depression, woman's preference for and satisfaction with treatment, QoL *For the baby*: peri-natal morbidity, macrosomia, gestation at delivery, birth weight centile corrected for gestational age, parity, ethnicity, maternal weight and fetal sex, birth trauma, hypoglycemia, measures of growth and neurodevelopment at childhood follow-up **Exclusion criteria** Quasi-RCTs	**Study characteristics** ***No. of included RCTs:*** 2 (published in 1986 and 1993) ***No. of included patients:*** 61 (47 T1DM, 14 T2DM) ***Duration of DM:*** NA ***Inclusion of patients with previous SH:*** NA ***Duration of follow-up*** *(months):* until delivery **Study quality** ***QA criteria:*** *Cochrane handbook* 1) Selection bias (allocation concealment) 2) attrition bias (loss of participants) 3) performance bias (blinding of participants, researchers and outcome assessment) ***QA results:*** 1) Selection bias: Only one study reported concealment method. 2) Attrition bias: Attrition rate ranged from 0 to 13% throughout one study; no to follow-up in the other study. 3) Performance bias: None reported blinding of outcome assessment.	**Safety** ***DKA:*** NA ***SH:*** No difference in maternal hypoglycemia between IPT and MDI ***Site infection:*** NA ***Pump malfunction:*** NA **Efficacy** ***A1C*** *(%):* no significant differences between IPT and MDI ***Patient satisfaction:*** NA ***QoL:*** NA ***Secondary complications of DM:*** NA **Pregnancy outcomes:** ***Birth weight:*** significantly increased in IPT group ***Macrosomia rate:*** no significant difference ***Other:*** no significant difference in any other outcome measures **Conclusion:** The data are limited because of the small number of trials appropriate for meta-analysis, small study sample size, and questionable generalizability of the trial population. Conclusion cannot be made from the data available.

*1) quarterly searches of the CENTRAL; 2) monthly searches of MEDLINE; 3) handsearches of 30 journals and the proceedings of major conferences; 4) weekly current awareness search of a further 37 journals

Table T.D.1: Summary of the included systematic reviews (cont'd)

Study	Study selection	Included studies	Results/conclusion
Mukhopadhyay 2007[39] Meta-analysis **Objective** To study the effects of IPT versus MDI in achieving glycemic control in pregnant diabetic women and to study the maternal and peri-natal outcomes **Search** ***Database searched:*** MEDLINE (1955 to April 2006), CENTRAL, CINAHL, EMBASE (1974 to April 2006) ***Other source:*** letters, editorials, and references in journal articles, manual search of textbooks	**Inclusion criteria** ***Study design:*** RCTs ***Population:*** pregnant diabetic women ***Intervention:*** comparison of IPT vs. MDI ***Outcome measures:*** at least one of the following: Diabetes-related: glycemic control, hypo- and hyperglycemic episodes requiring intervention, insulin dosage, diabetic complications Pregnancy-related: maternal complications, mode of delivery, neonatal complications, gestational age at delivery, preterm deliveries, birth weight, fetal anomalies, and maternal satisfaction/QoL **Exclusion criteria:** NA	**Study characteristics** ***No. of included RCTs:*** 6 (published between 1986 to 1993); 5 on T1DM ***No. of included patients:*** 213 (at least 177 with T1DM) ***Duration of DM:*** NA ***Inclusion of patients with previous SH:*** NA ***Duration of follow-up*** *(months):* until delivery **Study quality** ***QA criteria:*** 1) randomization, 2) group comparability, 3) inclusion criteria, 4) exclusion criteria, 5) intervention, 6) follow-up, 7) outcome quantification, 8) intention to treat analysis, 9) outcome assessment blind to treatment allocation, 10) both groups treated similarly except for the interventions ***QA results:*** Two trials were truly randomized and two trials were quasi-randomized; all with clear inclusion but without or no clear exclusion criteria; group comparable in five studies; none performed intention to treat analysis; loss to follow-up less than 10% in all studies	**Safety** ***DKA:*** more frequent in IPT group (nss) ***SH:*** more frequent in IPT group (nss) ***Infection:*** NA ***Pump malfunction:*** catheter disconnection: three in IPT group (one study); catheter leakage and occlusion occurred infrequently **Efficacy** ***A1C*** *(%):* improved in both groups from first trimester to term, no difference between the two groups in any time Pooled WMD: 0.10 (95% CI –0.12 to 0.33, P = 0.34) ***Patient satisfaction:*** NA ***QoL:*** NA ***Secondary complications of DM:*** rates of worsening retinopathy higher in IPT group (nss) **Pregnancy outcomes** ***Mode of delivery:*** nss in Caesarean section ***Preterm delivery:*** nss ***Birth weight:*** nss ***Stillbirth:*** 6.4% in IPT vs. 1.1% in MDI (nss) ***Neonatal hypoglycemia:*** nss **Conclusion:** No significant differences were found in pregnancy outcomes and glycemic control between IPT and MDI. The results did not demonstrate a clear-cut benefit of using IPT over MDI.

Table T.D.2: Summary of the included HTAs

Study	Study selection	Included studies	Summary/conclusion
Medical Advisory Secretariat 2009[40] **Objective** To review the efficacy of IPT as compared to MDI for patients with T1DM **Search** ***Database searched:*** MEDLINE (1966 to June 2008), EMBASE (1980 to 2008), CINAHL (1982 to June 2008), Cochrane Library, CRD Databases/International Agency for Health Technology Assessment Other source: reference lists	**Inclusion criteria** ***Study design:*** RCTs, SRs/meta-analyses, HTAs published between January 2000 and March 2009 ***Population:*** adult patients ≥ 19 years) with T1DM, currently on intensive insulin therapy ***Intervention:*** comparison on IPT vs. MDI Outcome measures: at least one of the following: glycemic control, hypo- and hyperglycemic episodes requiring intervention, insulin dosage, diabetic complications **Exclusion criteria** • Studies with < 20 patients • Studies < 5 weeks in duration • IPT only applied at nighttime and not 24 hours/day • Mixed group of patients (children, adults, T1DM, T2DM) • Prenancy study	**No. of included studies:** 7 SRs, 5 RCTs (one conference abstract) **Study quality** ***QA criteria:*** Quality assigned to individual studies: MAS's adaptation of the levels-of-evidence hierarchy[58] Overall quality of the evidence: GRADE Working Group criteria[59] ***QA results:*** Overall, the body of evidence was downgraded from high to low due to study quality and issues with directness as identified using the GRADE tool. Blinding of study personnel during outcome assessment and allocation concealment were generally lacking. Generalizability of studies was questionable as most trials included highly motivated patients with fairly good glycemic control. Evidence was very low for the outcome of hypoglycemia events.	There is conflicting evidence regarding both mild and severe hypoglycemic events in this population when using IPT as compared to MDI; these findings are based on very low-quality evidence. Based on low-quality evidence, IPT confers a statistically significant but not clinically significant reduction in A1C and mean daily glucose as compared to MDI in adults with T1DM (> 19 years). There is an improved QoL for patients using IPT as compared to MDI; however, limitations exist with this evidence.

Table T.D.2: Summary of the included HTAs (cont'd)

Study	Study selection	Included studies	Summary/conclusion
Campbell et al. 2008[41] **Objective** To provide a summary of the recent evidence pertaining to the relative effectiveness, safety, and cost-effectiveness of IPT in patients with T1DM as compared to optimized MDI **Search** ***Database searched:*** MEDLINE (January 2002 to August 2007), EMBASE (January 2002 to August 2007), Cochrane Library (January 2002 to August 2007), CRD databases ***Other source:*** reference lists of key papers	**Inclusion criteria** ***Study design:*** RCTs, ≥ 10 weeks in duration ***Population:*** patients (adults, children, adolescents) with T1DM, and pregnant women with pre-existing diabetes ***Intervention:*** IPT (any manufacturer) ***Comparator:*** optimized MDI (≥ 3 injections/day) ***Outcome measures:*** A1C levels, lipid levels, QoL, SH episodes, DKA episodes **Exclusion criteria** ***Population:*** newly diagnosed diabetes, gestational diabetes ***Intervention:*** implantable pumps, hospital inpatient pumps ***Comparator:*** conventional therapy	**No. of included studies:** 2 SRs, 5 RCTs (six publications) **Study quality** ***Dimensions of evidence:*** 1) strength of the evidence level, 2) quality, 3) statistical precision, 4) size of effect, and 5) relevance of evidence ***Quality criteria for SRs:*** 1) clear clinical question, 2) adequate search strategy, 3) appropriate inclusion criteria, 4) quality assessment of included studies, 5) appropriate summary of the characteristics and results of the individual studies, 6) appropriate methods for pooling the data, and 7) exploration of sources of heterogeneity ***Criteria for RCTs:*** 1) true randomization, 2) concealment of treatment allocation, 3) similarity in prognostic factors at baseline between the groups, 4) specified eligibility criteria, 5) presentation of the point estimate and measure of variability for the primary outcome measure, 6) intention-to-treat analysis, and 7) description of withdrawals and dropouts ***QA results:*** Many of the included studies were crossover in design and the issue of carryover was not appropriately addressed in the primary publications.	In adult patients with T1DM, SH episodes were infrequent in both trials but were consistently lower during treatment with IPT compared with MDI. DKA events were also uncommon but occurred more frequently during treatment with CSII than MDI. When compared with optimized MDI, IPT results in a modest but potentially worthwhile improvement in A1C levels in adult patients and children or adolescents with T1DM. Because of the short duration of the clinical trials it is not possible to evaluate the longer term benefits of such a difference in A1C levels. Although more immediate primary benefits from IPT may be associated with an impact on the incidence of SH events and improved QoL (through greater flexibility of lifestyle), there is limited evidence to support this from the studies identified in this update.

Table T.D.3: Insulin delivery system and type of insulin used in RCTs included in the eight systematic reviews

Study	Insulin pump	Type of insulin used	
		IPT	MDI
Fatourechi[31] (all ages)	**In studies published 2004 onward:** Animas, D-Tron, H-TronV-100, Medtronic MiniMed 508 (used most often), MiniMed 508, Paradigm 511, Disetronic H-Tron V100, or H-Tronplus V100 **In studies published between 1982 and 2003:** Tayco, Disetronic pump, H-Tronplus Disetronic, Medtronic 508, MiniMed 508, Medtronic MiniMed 507	Insulin lispro, insulin aspart	Insulin lispro/insulin glargine, insulin lispro/NPH, regular insulin/NPH, insulin aspart/insulin glargine, insulin aspart/NPH
Monami[34] (all ages)	NA	Insulin lispro, insulin aspart, unspecified short-acting analogue	Insulin lispro/insulin glargine, insulin lispro/NPH, insulin aspart/insulin glargine, insulin aspart/NPH, unspecified short-acting analogue/NPH, unspecified short-acting analogue/NPH/glargine
Pickup[35] (all ages)	NA	NA	NA
Jeitler[36] (all ages)	**In studies published 2004 onward:** HTr-V100, HTr-pl-V100 **In studies published between 1982 and 2003:** AS-6C, AS-6MP, AS-8MP, BTr-I + II, BTr-II, G-MS-36, HTr-D/V, HT-r V100, Med-209, Med-209-100, MHI, MHI-1001, MJ-MC-20, MM-506/507, Nor-I, Pro-E1	Regular insulin, insulin analogues	**In studies published 2004 onward:** analogue/glargine, analogue/NPH **In studies published between 1982 and 2003:** regular/NPH (used most often), analogue/NPH, regular/monotard, regular/ultralente, regular/
Church[37] (preschool children)	NA	NA	NA
Pankowska et al.[38] (children)	NA	NA	NA
Farrar[32] (pregnant women)	Microjet MC20, Microjet MC20/DehediBV	Porcine insulin (Actrapid MC)	Actrapid MC, regular/intermediate
Mukhopadhyay[39] (pregnant women)	**In studies published between 1986 and 1993:** Autosyringe (AS-SC, AS 6-C, AS 6-C[U-100], Lilly CPI-9100), Microjet MC20, Microjet MC20/DehediBV	NA	Regular insulin, intermediate/isophane/actrapid, intermediate/short-acting/retard

Table T.D.4: Evidence from new RCTs

Study	Patient group	Intervention	Results	Authors' conclusion
Bolli et al. 2009[42] Italy **Study design** Multicentre (N = 5), open label, parallel, prospective **Objective:** to assess the difference in glycemic control when patients with T1DM using NPH insulin-based MDI are randomized either to a MDI regimen with insulin glargine as basal insulin and mealtime insulin lispro, or to IPT with insulin lispro, and managed on either regimen for 6 months	**Total number:** 50 (IPT: 24 vs. MDI: 26) **Age** (yr): IPT: 37.6 ± 12.3 vs. MDI: 42.4 ± 9.9 **Gender** (M/F): IPT: 13/11 vs. MDI: 14/12 **BMI** (kg/m^2): IPT: 23.8 ± 2.7 vs. MDI: 24.3 ± 1.9 **Duration of DM** (yr): IPT: 18.5 ± 8.4 vs. MDI: 20.9 ± 10.6 **History of SH:** none **Previous pump use:** none **Baseline A1C** (%): IPT: 7.7 ± 0.7 vs. MDI: 7.8 ± 0.6 **Comorbidity:** NA **Secondary complications of DM:** none **Inclusion criteria:** age between 18 and 70 yrs, had T1DM > 1 yr, A1C between 6.5 to 9.0%, currently used MDI with NPH insulin **Exclusion criteria:** prior users of insulin pump or insulin glargine, unwilling or unable to use insulin pump or MDI, had > two SH events in the previous 6 months, had recent DKA or impaired hepatic/renal function	**Insulin pump:** MiniMed 508 pump (MiniMed Technologies, Northridge, CA) **Insulin** Basal-bolus: insulin lispro **Comparator – MDI** Basal: insulin glargine, once daily Bolus: insulin lispro, mealtime, three times daily **Duration of randomization:** 24 weeks preceded by 1-week run-in period **Follow-up:** 24 weeks	**Safety** IPT: 18 patients experienced 59 TEAEs vs. MDI: 22 patients experienced 56 TEAEs ***DKA:*** NA ***SH:*** two episodes in both groups ***Infection:*** one infusion site infection in IPT ***Pump malfunction:*** three patients had pump replaced without mechanical failure, 20 infusion set occlusions in nine patients **Efficacy** ***A1C*** (%)**:** IPT: decreased from 7.7 ± 0.7 at baseline to 7.0 ± 0.8 at 24 weeks vs. MDI: 7.8 ± 0.6 at baseline to 7.2 ± 0.7 at 24 weeks Difference between IPT and MDI at 24 weeks: −0.1% (95% CI −0.5 to 0.3; nss) ***Patient satisfaction*** (DTSQ score): increased more in IPT IPT: increased from 22.8 ± 8.1 to 31.5 ± 4.9 at 24 weeks vs. MDI: increased from 24.0 ± 6.3 to 28.8 ± 5.4 (treatment difference: 3.1 (95% CI 0.1 to 0.6; P = 0.042) ***QoL:*** NA ***Secondary complications of DM:*** NA	In unselected patients with T1DM naïve to IPT or MDI with insulin glargine, glycemic control is no better with the more expensive IPT compared to glargine-based MDI therapy.

Table T.D.4: Evidence from new RCTs (cont'd)

Study	Patient group	Intervention	Results	Authors' conclusion
Peyrot & Rubin 2009[6] United States **Study design** Two sites, parallel RCT **Objective:** to examine the effect of MDI and SMBG with glucose data management software (DMS) compared to an integrated system that combines 1) an insulin pump and bolus decision support software with 2) RT glucose monitoring with alarms for hypo- and hyperglycemia as an adjunct to SMBG and 3) glucose DMS on intermediate-term glucose control and assess patient-reported outcomes	**Total number:** 28 (IPT: 14 vs. MDI: 14) **Age** (yr): 47.2 ± 13.2 (range 25 to 70) **Gender** (M/F): 13/15 **BMI** (kg/m²): 27.0 ± 4.2 (range 20.2 to 37.3) **Duration of DM** (yr): 25.6 ± 12.6 (range 4 to 47) **History of SH:** NA **Previous pump use:** none **Baseline A1C** (%): 8.6 ± 1.0 (range 7.5 to 11.1) **Comorbidity:** NA **Secondary complications of DM:** NA **Inclusion criteria:** insulin pump naïve patients in suboptimal glycemic control **Exclusion criteria:** NA	**Insulin pump:** Paradigm 722 system (Medtronic MiniMed, Northride, CA) that combines a "smart" insulin pump with RT-CGM and CareLink™ DMS **Insulin used:** Basal-bolus: rapid-acting insulin analogues **Comparator – MDI** SMBG with glucose DMS Basal: not clear Bolus: rapid-acting insulin analogue **Duration of randomization:** 16 weeks **Follow-up:** 16 weeks	**Safety** ***DKA:*** 0 in IPT vs. 1 in MDI ***SH:*** 0 in IPT vs. 3 in MDI ***Infection:*** NA ***Pump malfunction:*** NA **Efficacy** ***A1C (%):*** IPT: reduced 1.7% (from 8.87 ± 0.89% to 7.16 ± 0.75, P < 0.001); MDI: reduced 1.0% (from 8.32 ± 1.05 to 7.30 ± 0.92, P = 0.002) Difference between IPT and MDI at 16 weeks: −0.7% (P = 0.071, nss) ***Patient satisfaction:*** (with BG monitoring system): patients in IPT reported significantly better scores on all measures of overall satisfaction/preference and rated the study BG monitoring system to be significantly superior to their pre-study system and would recommend it to others; they were neutral on whether they wanted to switch to another BG monitoring system or continue with the CGM system. Patient rating on insulin delivery system: 5 out of 7 items showed significant difference between changes in the two groups; at EOS, patients in IPT group reported significantly better scores on all three measures of overall satisfaction or preference and judged the study insulin delivery system to be significantly superior to their pre-study system, would recommend it to others, and would prefer to continue using it. User acceptance for study treatment system: the majority of the measures of DMS, CGM, and IPT were significantly different from neutral in the positive direction. ***QoL:*** NA ***Secondary complication of DM:*** NA	The integrated RT-CGM / insulin pump system was associated with physiological benefits over SMBG/MDI that would be clinically significant but that were not statistically significant because of the lack of statistical power associated with the small sample. Several patient-reported outcomes were significantly more positive in the study group than the control group; none was significantly more positive in the control group. Overall, participants preferred RT-CGM / IPT system over SMBG + MDI.

Table T.D.4: Evidence from new RCTs (cont'd)

Study	Patient group	Intervention	Results	Authors' conclusion
Thomas et al. 2007[28] United Kingdom **Study design** Pilot prospective trial **Objective:** to determine the potential for prevention of further SH and restoration of hypoglycemia awareness by rigorous avoidance of biochemical hypoglycemia employing optimized analogues regimen (MDI), IPT, and a control group remaining on existing insulin but given matching structured education	**Total number:** 21 (IPT: 7 vs. MDI: 7 vs. education with conventional insulin therapy: 7) **Age** (yrs): 43 ± 10 **Gender** (M/F)**:** 11/10 **BMI** (kg/m^2): NA **Duration of DM** (yr): 25 ± 10 **History of SH:** all had SH and altered hypoglycemia awareness **Previous pump use:** none **Baseline A1C** (%): IPT 8.5 ± 1.9 vs. MDI 8.6 ± 1.1 **Comorbidity:** four patients had abnormal sweating; none had gastroparesis/postural hypotension **Secondary complications of DM:** 14 (71%) retinopathy, 3 (43%) nephropathy, 11 (52%) peripheral neuropathy, 4 (19) atherosclerotic vascular disease **Inclusion criteria:** had ≥ 1 SH episode in previous 6 months; naïve to MDI insulin analogue therapy **Exclusion criteria:** NA	**Insulin pump:** MiniMed 508 (Medtronic) **Insulin:** Basal-bolus: insulin lispro **Comparator – MDI** Basal: pre-evening meal insulin glargine Bolus: pre-meal insulin lispro **Duration of randomization:** 24 weeks **Follow-up:** 24 weeks	**Safety** ***DKA:*** none ***SH:*** reduced in both groups; 3 in IPT vs. 2 in MDI (nss) ***Infection:*** no injection site infection ***Pump malfunction:*** NA **Efficacy** ***A1C (%):*** IPT: from 8.5 ± 1.9 at baseline to 7.4 ± 1.0 at 24 weeks (P = 0.06) MDI: from 8.6 ± 1.1 at baseline to 7.6 ± 0.7 at 24 weeks (P = 0.04) Difference between IPT and MDI at 24 weeks: −0.1% (nss) ***Patient satisfaction:*** NA ***QoL:*** *DQoL score:* IPT: from 69 ± 19 at baseline to 74 ± 20 at 24 weeks (P = 0.11) MDI: from 47 ± 20 at baseline to 70±11 at 24 weeks (P = 0.14) *HFS:* IPT: from 67 ± 19 at baseline to 64±16 at 24 weeks (P = 0.21) MDI: from 91 ± 21 at baseline to 83±126 at 24 weeks (P = 0.06) ***Secondary complications of DM:*** NA	This pilot RCT comparing optimized MDI, IPT, or education alone in unselected individuals with recurrent severe hypoglycemia showed potential for restoring hypoglycemia unawareness and preventing further severe hypoglycemia with concomitant improvement in glycemic control in MDI and IPT groups.

Table T.D.4: Evidence from new RCTs (cont'd)

Study	Patient group	Intervention	Results	Authors' conclusion
Nabhan et al. 2009[43] United States **Study design** Single centre, partial crossover (patients assigned to IPT remained in IPT group, whereas patients assigned to MDI switched to IPT after 6 months of randomization) **Objective:** to compare glycemic control, BMI, neuro-cognitive function, and presenting stress for preschool-aged diabetic children randomized to treatment either with IPT or with MDI	**Total number:** 42 (IPT: 21 vs. MDI: 21) **Age** (yr)**:** IPT: 3.8 ± 0.8 vs. MDI: 3.7 ± 0.7 (P > 0.05)* **Gender (M/F)*:** IPT: 10/11 vs. MDI: 7/14* **BMI** (% for age): IPT: 77.8 ± 21.7 vs. MDI: 79.7 ± 17.9* **Duration of DM** (yr): IPT: 1.8 ± 0.6 vs. MDI: 1.8 ± 0.6 (P>0.05)* **History of SH:** NA **Previous pump use:** none **Baseline A1C** (%): IPT: 9.0 ± 0.6 vs. MDI: 9.0 ± 0.6 (P > 0.05)* **Comorbidity:** none **Secondary complications of DM:** none **Inclusion criteria:** < 5 yr, history of T1DM ≥ 12 months, one or more insulin injections daily, families with a history of good compliance with physician visit and home glucose monitoring **Exclusion criteria:** children with medical conditions that required medications known to affect blood glucose	**Insulin pump*:** MiniMed 508 (Medtronic MiniMed, Northridge, CA) **Insulin** Basal-bolus: insulin lispro **Comparator – MDI*** Long-acting insulin including NPH (10), lente (2), glargine (1) Short-acting: insulin lispro (all patients) Frequency: two injections daily in 15 children and three or more injections in two children **Duration of randomization:** 6 months **Follow-up:** 12 months (35 children completed the study, 18 in IPT and 17 in MDI)	**Safety*** ***DKA:*** none ***SH:*** 1 in IPT vs. 1 in MDI ***Infection:*** no significant site infection ***Pump malfunction:*** NA **Efficacy** ***A1C (%):*** decreased in both groups (8.9 ± 0.6 at baseline vs. 8.5 ± 0.7 at 12-month (P = 0.006) In IPT group (n = 18), decreased 0.4% at 3 months, but increased 0.1% at 6 months; decreased from baseline 8.8 ± 0.6 to 8.5 ± 0.6 at 12 months, P = 0.4) Difference between IPT and MDI at 6 months: −0.2% (IPT 8.5 ± 0.6 vs. MDI 8.7 ± 0.7, nss)* ***Patient satisfaction:**** children and families are pleased with IPT, evidenced by a very low rate of pump discontinuation. After 6 months of pump use, 19/20 (95%) opted to continue IPT ***QoL:*** not measured ***Secondary complications of DM:*** NA **Neuro-cognitive function and child behaviour changes:** No statistically significant differences between the two groups	Initiation of IPT versus continuing MDI does not significantly influence A1C, neuro-cognitive, or parenting stress and child behaviour parameters in a research study setting. IPT and MDI achieved similar results in mean A1C, neuro-cognitive, parenting, and child behaviour functioning after 1 year of treatment. These data may help establish realistic expectations of IPT in very young children with diabetes.

* Based on an earlier publication[60]

Table T.D.4: Evidence from new RCTs (cont'd)

Study	Patient group	Intervention	Results	Authors' conclusion
Nuboer et al. 2008[44] Netherlands **Study design:** single centre, open, prospective parallel RCT **Objective:** to investigate the effects of IPT vs. MDI in children with T1DM with regards to QoL and impact of disease as well as adverse effects and parameters of metabolic control	**Total number:** 38 (IPT: 19 vs. MDI: 19) **Age** (yr): IPT: 10.0 ± 3.0 vs. MDI: 10.0 ± 3.7 **Gender** (M/F): IPT: 7/12 vs. MDI: 10/9 **BMI** (kg/m^2): NA **Duration of DM** (yr): IPT: 5.6 ± 3.3 vs. MDI: 4.7 ± 2.9 **History of SH:** 10 patients **Previous pump use:** none **Baseline A1C** (%): IPT: 7.66 ± 0.56 vs. MDI: 7.98 ± 0.57 **Comorbidity:** not applicable **Secondary complications of DM:** not applicable **Inclusion criteria:** T1DM, diagnosed by the presence of islet antigen-2, glutamic acid decarboxylase-65 or islet cell cytoplasmic autoantibodies, daily insulin administration ≥ 1 yr, random c-peptide < 200 pmol, A1C > 8.0%, a history of repeated symptomatic hypoglycemia, age 4 to 16 yrs **Exclusion criteria:** clinically manifested chronic complications, pregnancy, comorbidity, mental retardation, psychiatric treatment or symptoms in a child or parent, insufficient Dutch language capability, and absence of a telephone at home	**Insulin pump:** H-Tron Disetronic insulin pumps (Roche, Basel, Switzerland) **Insulin:** Basal-bolus: insulin aspart **Comparator – MDI** **MDI:** 3.5-month run-in phase for all children: Basal: NPH or glargine for bed time injection Bolus: three rapid- or short-acting insulin before breakfast, lunch, and supper; 26 used insulin aspart, 12 used regular insulin **Duration of randomization:** 3.5 months **Follow-up:** 3.5 months ± 1 week	**Safety** ***DKA:*** IPT: 2 vs. MDI: 4 times ***SH:*** IPT: 2 episodes vs. MDI: 4 episodes during randomization; mean 1.1 per patient year for MDI vs. 0.29 per patient year for IPT (3-fold decrease) ***Infection:*** NA ***Pump malfunction:*** NA **Efficacy** ***A1C*** (%): 8.34± 0.93 before run-in vs. 7.82 ± 0.58 after run-in (–0.52%, P = 0.001) (N = 38) Difference between IPT and MDI at 3.5 months: –0.16% at (unclear statistical significance) ***Patient satisfaction:*** NA ***QoL:*** PedsQL scores increased significantly during the run-in phase (P = 0.006 for parents and P = 0.001 for children); remained stable while on MDI in the randomization phase and increased nonsignificantly while on IPT. Impact of disease score: Decreased nonsignificantly during run-in phase, and randomization phase. **Secondary complications of DM**: NA ***Neuro-cognitive function and child behaviour changes:*** NA	A 3-fold decrease in SH was observed in the IPT phase of this study and quality of life and impact of disease scores were shown to improve by IPT when within-patient analyses were performed but not when treatment groups were compared.

Table T.D.4: Evidence from new RCTs (cont'd)

Study	Patient group	Intervention	Results	Authors' conclusion
Skogsberg et al. 2008[22] Sweden **Study design** Open, randomized, parallel, multicentre (nine pediatric departments) trial **Objective:** to compare safety, metabolic control, and treatment satisfaction in children and adolescents at onset of T1DM who were treated with IPT or MDI	**Total number:** 72 (IPT: 34 vs. MD I: 38) **Age** (yr): IPT 11.8 ± 4.9 vs. MDI 12.3 ± 4.5 (P = 0.47) **Gender** (M/F): 42/30 **BMI** (kg/m²): no significant difference between the groups **Duration of DM:** ≤ 3 weeks **History of SH:** none **Previous pump use:** none **Baseline A1C** (%): IPT 8.2 ± 0.4 vs. MDI 8.4 ± 0.5 (P = 0.57) **Comorbidity:** none **Secondary complications of DM:** not applicable **Inclusion criteria:** newly diagnosed children and adolescents with T1DM **Exclusion criteria:** NA	**Insulin pump:** H-Tron (Roche, Burgdorf, Switzerland) **Insulin** Basal-bolus: insulin aspart **Comparator – MDI** Basal: NPH twice daily (morning and bedtime) by pen Bolus: insulin aspart 3 to 4 times daily by pen **Duration of randomization:** 24 months **Follow-up:** 24 months (67 completed the whole study, five in MDI group did not complete the study: two switched to IPT later, two switched to long-acting insulin glargine, one dropped out at 12 months.)	**Safety** ***DKA:*** none in both groups ***SH:*** IPT 13 vs. MDI 12 during study period (nss) ***Infection:*** not reported ***Pump malfunction:*** technical problem (not specified): 5 in IPT group and 1 in MDI group **Efficacy** ***A1C*** (%): at 24 months: IPT: 6.5 ± 0.4 vs. MDI: 6.7 ± 0.5 (P = 0.66) Difference between IPT and MDI at 24 months: 0% ***Treatment satisfaction*** (DTSQ score): At 1 month: IPT: 31.5 ± 1.4 vs. MDI: 28.4±1.8 (P = 0.01) At 24 months: IPT: 33.1 ± 0.9 vs. MDI: 27.5 ± 2.0 (P < 0.001) ***QoL:*** NA ***Secondary complications of DM:*** NA ***Neuro-cognitive function and child behaviour changes:*** NA	Insulin pump therapy proved to be a safe therapy in children and adolescents followed for 24 months after onset of their diabetes. Treatment satisfaction was higher in the IPT group, although there was no difference in metabolic control compared with the MDI group.

Table T.D.5: Insulin pumps and types of insulin used in the new RCTs

Study	Insulin pump	Type of insulin used	
		IPT	MDI
Bolli et al. 2009[42]	MiniMed 508 pump(MiniMed Technologies, Northridge, CA)	Basal-bolus: insulin lispro	Basal: insulin glargine Bolus: insulin lispro
Peyrot & Rubin 2009[6]	Paradigm 722 system (Medtronic MiniMed, Northridge, CA)	Basal-bolus: unclear	Basal-bolus: unclear
Thomas et al. 2007[28]	MiniMed 508 (Medtronic)	Basal-bolus: insulin lispro	Basal: glargine Bolus: insulin lispro
Nabhan et al. 2009[43]	MiniMed 508 (Medtronic, Northridge, CA)	Basal-bolus: insulin lispro	Basal: NPH, lent, glargine Bolus: insulin lispro
Nuboer et al. 2008[44]	H-Tron Disetronic insulin pumps (Roche, Basel, Switzerland)	Basal-bolus: insulin aspart	Basal: NPH, glargine Bolus: insulin aspart, regular insulin
Skogsberg et al. 2008[22]	H-Tron Disetronic insulin pumps (Roche, Burgdorf, Switzerland)	Basal-bolus: insulin aspart	Basal: NPH Bolus: insulin aspart

Note: Only one RCT[22] mentioned the use of pens as the delivery system for MDI

Table T.D.6: Training/education and equipments required

Study	Training/education	Availability care team	Equipment required
Bolli[42]	NA	NA	NA
Peyrot & Rubin 2009[6]	**MDI group:** ***General:*** diet, exercise, BG and acute crisis management, BG and ketone testing, and use of the DMS; 2 to 4 hrs **IPT group:** ***General:*** same as MDI group ***Specific:*** use of RT-CGM/CSII system; 4 to 5 hrs	NA	NA
Thomas 2007[28]	Equivalent education and support to all patients with a single additional training session for those in IPT group (technical aspects of pump management)	NA	Self-measured capillary blood glucose was determined using a whole blood-calibrated One-Touch Basic glucosemeter (LifeScan, High Wycombe, UK).
Nabhan 2009[43]	Half-day education before randomization: insulin types, insulin adjustment, and carbohydrate counting were reviewed* Second education session with a nurse educator after randomization*	BG measures sent at least weekly, and insulin adjustments were made by the principal investigator. For the first 3 to 4 weeks, families of children were given 24-hr access to the principal investigator. For the first 10 days, the principal investigator contacted caregivers daily to make insulin adjustment.	All families were asked to monitor BG levels prior to each ACCU-CHEK complete meter (Roche Diagnostics, Indianapolis, IN); all families were provided with Acculink fax-modems to facilitate weekly insulin adjustments*.
Nuboer 2008[44]	NA	Diabetes team available 24 hrs by phone.	New and carefully calibrated Precision Xtra (Abbott, Alameda, CA) equipment used for capillary blood glucose measurement. Capillary blood samples were sent to the national standardization lab for determination of by high-performance liquid chromatography.
Skogsberg 2008[22]	**IPT group:** by the pediatric diabetes team according to the national guidelines; half day on operating the insulin pump **MDI group:** by the pediatric diabetes team according to the national guidelines	Telephone contact could occur on a more frequent basis (no details provided). A pediatric diabetes team followed patients regularly (no details).	A1c was analyzed at the central lab, using a high-performance liquid chromatography method (Bio-Rad Laboratories, Hercules, CA), calibrated according to the Swedish national reference.

*based on an earlier publication[60]

References

1. Potti LG, Haines ST. Continuous subcutaneous insulin infusion therapy: a primer on insulin pumps. *Journal of the American Pharmacists Association* 2009;49(1):e1-e13.
2. Shalitin S, Phillip M. The use of insulin pump therapy in the pediatric age group. *Hormone Research* 2008;70(1):14-21.
3. Skryabina E, Davey C, Wilson S, Chan J. *Buyer's guide: insulin pumps*. London, United Kingdom: Centre for Evidence-based Purchasing, NHS; 2008. Report No.: CEP 08004.
4. Heinemann L. Future directions in insulin therapy and treatment of diabetes mellitus: a critical comment. *Clinical Cornerstone* 2007;8(2):66-74.
5. Bruttomesso D, Costa S, Baritussio A. Continuous subcutaneous insulin infusion (CSII) 30 years later: still the best option for insulin therapy. *Diabetes Metabolism Research & Reviews* 2009;25(2):99-111.
6. Peyrot M, Rubin RR. Patient-reported outcomes for an integrated real-time continuous glucose monitoring/insulin pump system. *Diabetes Technology & Therapeutics* 2009;11(1):57-62.
7. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Canadian Journal of Diabetes* 2008;32(Suppl 1):S1-S201.
8. Hirsch IB. Insulin analogues. *New England Journal of Medicine* 2005;352(2):174-83.
9. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *Canadian Medical Association Journal* 2009;180(4):385-97.
10. Retnakaran R, Hochman J, DeVries JH, Hanaire-Broutin H, Heine RJ, Melki V, et al. Continuous subcutaneous insulin infusion versus multiple daily injections: the impact of baseline A1C. *Diabetes Care* 2004;27(11):2590-6.
11. Steck AK, Klingensmith GJ, Fiallo-Scharer R. Recent advances in insulin treatment of children. *Pediatric Diabetes* 2007;8:49-56.
12. Tamborlane WV, Swan K, Sikes KA, Steffen AT, Weinzimer SA. The renaissance of insulin pump treatment in childhood type 1 diabetes. *Reviews in Endocrine & Metabolic Disorders* 2006;7(3):205-13.
13. National Institute for Health and Clinical Excellence (NHS). *Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus: review of technology appraisal guidance 57*. London: National Institute for Health and Clinical Excellence (NICE); 2008. 30 p. Report No.: TA151.
14. Magnolti MA. An update on insulin injection devices. *Insulin* 2007;2(4):173-81.
15. Phillip M. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2007;30(6):1653-62.
16. Health Canada. Medical Devices Active Licence Listing [cited 2009 Jul 29]. Available from: *http://mdall.ca*.

17. Smiths Medical. Smiths Medical announces intent to stop selling Deltec Cozmo Insulin Pumps. Ashford, UK: Smiths Medical; 2009 Mar 25 [cited 2009 Sep 17]. Available from: *http://www.smiths-medical.com/tools/print cfm?url.*

18. Health Canada. Drug Product Database 2009. Available from: *http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp.*

19. Ontario Ministry of Health and Long-Term Care. Questions and answers: insulin pump therapy. Toronto: Ontario Ministry of Health and Long-Term Care; 2009 Mar 24 [cited 2009 Mar 31]. Available from: *http://www.health.gov.on.ca/english/public/program/adp/insulin_pump_faq.html.*

20. Pickup JC. Are insulin pumps underutilized in type 1 diabetes? Yes. *Diabetes Care* 2006;29(6):1449-55.

21. Hanas R. CSII in children with diabetes. *Acta Biomedica* 2005;76(Suppl 3):36-8.

22. Skogsberg L, Fors H, Hanas R, Chaplin JE, Lindman E, Skogsberg J. Improved treatment satisfaction but no difference in metabolic control when using continuous subcutaneous insulin infusion vs. multiple daily injections in children at onset of type 1 diabetes mellitus. *Pediatric Diabetes* 2008;9(5):472-9.

23. Berghaeuser MA, Kapellen T, Heidtmann B, Haberland H, Klinkert C, Holl RW, et al. Continuous subcutaneous insulin infusion in toddlers starting at diagnosis of type 1 diabetes mellitus: a multicenter analysis of 104 patients from 63 centres in Germany and Austria. *Pediatric Diabetes* 2008;9(6):590-5.

24. Hanas R, Ludvigsson J. Hypoglycemia and ketoacidosis with insulin pump therapy in children and adolescents. *Pediatric Diabetes* 2006;7(Suppl 4):32-8.

25. Guilhem I, Leguerrier AM, Lecordier, Poirier JY, Maugendre D. Technical risks with subcutaneous insulin infusion. *Diabetes Metabolism* 2006;32(3):279-84.

26. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 1997;46(2):271-86.

27. Pedersen-Bjergaard U, Pramming S, Heller SR, Wallace TM, Jorgensen HV, Matthers DR, et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. *Diabetes Metabolism Research & Reviews* 2004;20(6):479-86.

28. Thomas RM, Aldibbiat A, Griffin W, Cox MA, Leech NJ, Shaw JA. A randomized pilot study in Type 1 diabetes complicated by severe hypoglycaemia, comparing rigorous hypoglycaemia avoidance with insulin analogue therapy, CSII or education alone. *Diabetic Medicine* 2007;24(7):778-83.

29. 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 England Journal of Medicine* 1993;329(14):977-86.

30. Fanelli CG. Counterregulatory responses in CSII. *Diabetes Research and Clinical Practice* 2006;74(Suppl 2):S108-S111.

31. Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of

continuous subcutaneous insulin infusion versus multiple daily injections. *Journal of Clinical Endocrinology & Metabolism* 2009;94(3):729-40.

32. Farrar D, Tuffnell DJ, West J. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. *Cochrane Database Systematic Reviews* 2007;(3):CD005542.

33. Cochrane Collaboration. *The Cochrane Collaboration's tool for assessing risk of bias*. 2009 [cited 2009 Oct 19]. Available from: *http://www.ohg.cochrane org/forms/Risk%20of%20bias%20assessment%20tool.pdf* 2009 [accessed 2009 Oct 19].

34. Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis. *Acta Diabetologia* (Online) 2009 Jun 6 [Epub ahead of print]. DOI: 10.1007/s00592-009-0132-5.

35. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabetic Medicine* 2008;25(7):765-74.

36. Jeitler K, Horvath K, Berghold A, Gratzer TW, Neeser K, Pieber TR, et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia* 2008;51(6):941-51.

37. Churchill JN, Ruppe RL, Smaldone A. Use of continuous insulin infusion pumps in young children with type 1 diabetes: a systematic review. *Journal of Pediatric Health Care* 2009;23(3):173-9.

38. Pankowska E, Blazik M, Dziechciarz P, Szypowska A, Szajewska H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. *Pediatric Diabetes* 2009;10(1):52-8.

39. Mukhopadhyay A, Farrell T, Fraser RB, Ola B. Continuous subcutaneous insulin infusion vs. intensive conventional insulin therapy in pregnant diabetic women: a systematic review and metaanalysis of randomized, controlled trials. *American Journal of Obstetrics and Gynecology* 2007;197(5):447-56.

40. Medical Advisory Secretariat. *Continuous subcutaneous insulin infusion (CSII) pumps for type 1 and type 2 adult diabetic populations: an evidence-based analysis*. Toronto: ON: Medical Advisory Secretariat and Ministry of Health and Long-Term Care; 2009 October. Report No.: Ontario Health Technology Assessment Series 2009;9(20).

41. Campbell S, Suebwongpat A, Standfield L, Weston A. *Systematic review update and economic evaluation for the New Zealand Setting: subcutaneous insulin pump therapy*. Christchurch: New Zealand: Health Services Assessment Collaboration (HSAC); 2008. Report No.: 1(3).

42. Bolli GB, Kerr D, Thomas R, Torlone E, Gazagnes S, Vitacolonna E, et al. Comparison of a multiple daily insulin injection regime (basal once-daily glargine plus mealtime lispro) and CSII (lispro) in type 1 diabetes: a randomized open parallel multicenter study. *Diabetes Care* [Internet]. 2009 Apr 23;32(7):1170-6. DOI: 10.2337/dc08-1874.

43. Nabhan ZM. A randomized prospective study of insulin pump vs. insulin injection therapy in very young children with type 1 diabetes: 12-month glycemic, BMI, and neurocognitive outcomes. *Pediatric Diabetes* 2009;10(3):202-8.

44. Nuboer R, Borsboom GJ, Zoethout JA, Koot HM, Bruining J. Effects of insulin pump vs. injection treatment on quality of life and impact of disease in children with type 1 diabetes mellitus in a randomized, prospective comparison. *Pediatric Diabetes* 2008 28;9(4 Pt 1):291-6.

45. Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N. Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. *Health Technology Assessment* (Winchester, UK) 2004;8(43):iii-171.

46. Centre for Evidence Based Medicine (McMaster University). *Levels of evidence*. 2009 Mar [cited 2009 Sep 30]. Available from: *http://mwhc-ebn.mcgill.ca/EBN_tools.htm*.

47. Cook DJ, Mulrow CD, Haynes RB. Synthesis of best evidence for clinical decisions. *Annals of Internal Medicine* 1997;126(5):376-80.

48. Bradley CF, Speight J. Patient perceptions of diabetes and diabetes therapy: assessing quality of life. *Diabetes Metabolism Research & Reviews* 2002;18(Suppl 3):S64-9.

49. Australasian Paediatric Endocrine Group for the Department of Health and Ageing. *Clinical practice guidelines: type 1 diabetes in children and adolescents*. Canberra: Australia: National Health and Medical Research Council (NHMRC); 2005.

50. National Collaborating Centre for Women's and Children's Health. *Diabetes in pregnancy - management of diabetes and its complications from preconception go the postnatal period*. London: RCOG Press at the Royal College of Obstetricians and Gynaecologists; 2008.

51. American Diabetes Association. Standards of medical care in diabetes–2009. *Diabetes Care* 2009;32(Suppl 1):S13-S61.

52. Egger M, Dickersin K, Davey Smith G. Problems and limitations in conducting systematic reviews. *BMJ* 2001:43-68.

53. Fisher LK. The selection of children and adolescents for treatment with continuous subcutaneous insulin infusion (CSII). *Pediatric Diabetes* 2006;7(Suppl 4):11-4.

54. Cogen FR, Henderson C, Hansen JA, Streisand R. Pediatric quality of life in transitioning to the insulin pump: does prior regimen make a difference? *Clinical Pediatrics* 2007;46(9):777-9.

55. Higgins JPT GS. *Cochrane handbook for systematic reviews of interventions 4.2.4*. Chichester, UK: John Wiley & Sons; 2005 Mar. Report No.: Issue 2.

56. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clinical Trials* 1996;17:1-12.

57. Schulz KF, Chalmers I, ayes RJ, ltman DG. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273(5):408-12.

58. Goodman C. *Literature searching and evidence interpretation for assessing health care practices*. Stockholm, Sweden: 1993.

59. Atkins D, Best D, Briss PA, Eccles M, Falck Ytter Y, Flottorp S, et al. GRADE Working Group: grading quality of evidence and strength of recommendations. *BMJ* 2004;328(7454):1490.

60. DiMeglio LA, Pottorff TM, Boyd SR, France L, Fineberg N, Eugster EA. A randomized, controlled study of insulin pump therapy in diabetic preschoolers. *Journal of Pediatrics* 2004;145(3):380-4.

SECTION THREE: ECONOMIC ANALYSIS (E)

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Objectives and Policy Questions

Objective

The objective of the economic analysis is to inform the economic impact of replacing multiple daily injections with insulin pump therapy for eligible patients with T1DM in Alberta.

Policy Questions

The economic analysis is to inform the following questions:

1. cost comparisons (effectiveness or utility analyses) of new technology in comparison to standard technology;
2. potential for transfer of service and funds from existing services being replaced or reduced in usage, as well the impact on the health system of such transfers;
3. estimates of patient and public demand, including prevalence and incidence of condition(s); utilization rates of standard or alternative treatments, where data exist; and estimates of the use of the new technology taking into account service capacity, *where feasible*, as well as appropriate clinical indicators for use;
4. total costs based on utilization estimates;
5. unit cost estimates, including physician billings, hospitalization or facility operational costs, other service costs, and capital costs for the procedure as well as related health services; and
6. costs of services avoided within a reasonable period of time.

Methodology

A literature review and synthesis was conducted to inform questions 1, 2, and 6. An analysis of administrative health data was conducted to inform questions 5. A budget impact analysis was conducted to inform questions 3 and 4.

Review of economic studies

Search strategy

Selected databases were searched for economic evaluation studies of IPT published from 1999 to June 2009. Core Databases searched included MEDLINE, EMBASE, EconLit, CINAHL, and Web of Science, along with the Cochrane Database of Systematic Reviews (CDSR) and the Centre for Reviews and Dissemination Databases (DARE, NHS EED, and HTA). The medical subject headings (MeSH) terms relevant to this topic are: Insulin Infusion Systems; Diabetes Mellitus, Type 1; Costs and Cost Analysis; and Cost-Benefit Analysis. Refer to Table E.A.1 (see Appendix E.A for detailed search strategy).

Selection criteria

The search was limited to human and English-language publications. Studies investigating the economic, health service utilization or cost impact of insulin pump therapy on the health system were included. Opinion articles (e.g., opinions or letters to the editor) and abstracts were excluded.

Selection of potentially relevant studies was reviewed by two reviewers independently. Disagreements were resolved through consensus between the two reviewers.

Quality assessment criteria

An informal quality assessment of economic studies was conducted using criteria adapted from Drummond et al.[1] The purpose of providing a quality assessment of economic studies in this report is to explicitly identify the components included and excluded in the studies and to provide a general assessment of the quality of the economic studies reviewed. The quality of potentially relevant studies was assessed by two reviewers independently.

Administrative database analysis

An analysis of provincial administrative health databases was conducted to estimate the impact of T1DM on inpatient, outpatient, and physician resources.

Source of information

Information on costs and resource utilization were retrieved from three administrative health databases. The Alberta Physician Claims database provided information related to billing services to physicians for medically insured services in Alberta. The Alberta Discharge Abstracts database provided information related to hospital inpatient procedures, whereas the Ambulatory Care Classification database provided information related to outpatient procedures.

Classifying type 1 diabetes mellitus in Alberta

Note that in the Alberta Physician Claims database a large majority of the diagnostic coding does not differentiate T1DM from T2DM. Furthermore, in all three databases the diagnostic coding does not differentiate between type 1 and type 2 gestational diabetes for pregnant women. Accordingly, patients with T1DM in the administrative health databases were identified using a direct and indirect approach.

In the direct approach, patients were diagnosed as having T1DM if they had an international classification of diseases (ICD) diagnosis code that was contained in any one of the three databases and directly corresponded to T1DM in any diagnosis filed. Classification codes are shown in Table E.1.

In the indirect approach, for the remaining patient population, patients are first defined as having undifferentiated diabetes. This was conducted using the National Diabetes Surveillance System definition[2] for diagnosing general diabetes. According to this definition, patients are diagnosed as having diabetes if they have at least two general ICD diabetes codes (e.g., ICD code 250) within 2 years. Within this population estimates of T1DM, calculated from the Canadian Community Health Survey 3.1, are applied to estimate the proportion of T1DM. According to the Canadian Community Health Survey, 12.6% of Albertans who reported having diabetes were taking insulin therapy within 1 month after diagnosis.[1]

[1] Patients with type 1diabetes typically initiate insulin therapy at the time of diagnosis, whereas those with type 2 diabetes do not immediate initiate insulin therapy

Table E.1: ICD code description for type 1 diabetes mellitus

ICD-10	ICD-9	Description
	250	Diabetes mellitus
E10. ×[a]	250. ×1	Insulin-dependent diabetes mellitus
	250. ×3	
O24. ×	648.0× 648.8×	Diabetes mellitus in pregnancy

[a]: The symbol × refers to any possible digit

Calculating the resource impact of type 1 diabetes mellitus

For each patient with a diagnosis of T1DM, the total costs of physician, inpatient, and outpatient services are calculated over the year (e.g., 2006/2007). The average cost of T1DM is calculated by summing the total costs across all patients with T1DM divided by the number of patients with T1DM. Calculating the average cost of T1DM is conducted for each target population.

Budget impact analysis

A budget impact analysis was conducted to determine the cost impact of IPT for preschool children, adolescents, adults, and pregnant women with T1DM in Alberta. Estimates for patient demand and utilization rates of available treatments in Alberta were combined with the cost of the technologies to estimate the cost associated with IPT compared to MDI. The analysis is conducted from a payer's perspective and considers only the costs of implementing IPT. The budget impact analysis is conducted separately for adults, pregnant women, children and adolescents, and preschool children.

Time horizon

The budget impact analysis has a 3 year time horizon[3] with the analysis broken down by year (2009, 2010, and 2011). It is assumed that all eligible patients will shift from MDI to IPT within the time horizon. Note that there are no data available to indicate the proportion of eligible patients who will transition to IPT in any given year. Hence, the analysis assumes that one-third of eligible patients will transition in each year. It is important to note that the analysis does not account for the proportion of patients on IPT who revert to MDI. However, alternative transition rates from MDI to IPT will be tested in a sensitivity analysis.

Demand and utilization estimates

Demand and utilization estimates were calculated from the three provincial administrative health databases described previously (data spanning from 2005/2006 to 2007/2008). Estimating the demand and utilization estimates from the administrative health databases for Alberta involves three primary STEs (see Table E.B.1 in Appendix E.B for further details):

1. estimating the number of patients in the databases who have T1DM, which is described in section 5.2.2;
2. forecasting the number of new cases of T1DM in years 2009 to 2011; and
3. estimating the number of patients with T1DM who are eligible for IPT and who switch to IPT in years 2009 to 2011.

Forecasting the Number Patients with Type 1 Diabetes Mellitus in 2009 to 2011

The number of patients identified as having T1DM from both direct and indirect methods outlined in section 5.2.2 provided an estimate for the total number of patients with T1DM for each population group between 2005 and 2008 in Alberta. These data were used to estimate the incidence rate for T1DM in order to forecast the number of patients with T1DM in 2009 to 2011 in Alberta by each population group (see Table E.B.1 in Appendix E.B).

The Proportion of Patients Eligible for Insulin Pump Therapy

All patients with T1DM are not ideally suited for IPT and only a proportion of patients with T1DM will become IPT users. Estimates published in the available literature report an uptake of IPT ranging between 2%[4] and 12%.[5] Note that there are no published empirical data informing the number of patients who are suited for IPT in Alberta.

Data from the Alberta Children's Hospital indicated an uptake of IPT of 11.7% in children (Allison Husband, Diabetes Clinic, Alberta Children's Hospital, personal communication, 31 August 2009). The uptake of IPT in adults in Alberta has been estimated at 5% in adults (Dr. Alun Edwards, University of Calgary, personal communication, 14 December 2009). Based on these estimates, we assume 5% of adults and pregnant women and 11.7% of children and adolescents will transition to IPT.

Budget impact calculation

Calculating the budget impact consists of multiplying the cost difference by the number of patients who switch from MDI to IPT in each of the population groups of interest. Table E.3 shows the costs associated with MDI and IPT respectively. This budget impact analysis was conducted under two scenarios. The first scenario considers costs associated with the technologies (i.e., all costs listed in Table E.3), whereas the second includes only the costs associated with the device for IPT (i.e., insulin pump, pump accessories, and patient education or training).

Pump costs data were collected from information provided by pump manufacturers. Costs for patient education and pump accessories (e.g., reservoir or cartridge and infusion set) were provided by clinician experts and were based on data from the Alberta Children's Hospital (Allison Husband, Diabetes Clinic, Alberta Children's Hospital, personal communication, 17 November 2009).

Insulin costs associated with MDI use were obtained from a recently published Canadian study.[6] Insulin costs associated with IPT were based on data from the Alberta Children's Hospital, which indicated that patients on IPT use 20% less insulin than those on MDI. The unit costs of lancets and test strips were based on their respective retail costs. Note that the total cost of consumables for patients on MDI was calculated assuming that patients on MDI would receive insulin injections and perform glucose testing an average of four times each day. The total cost of consumables for patients on IPT was calculated by assuming that the consumption of consumable items is increased by 25% when on IPT compared to MDI (Allison Husband, Diabetes Clinic, Alberta Children's Hospital, personal communication, 17 November 2009).

Literature Review Findings

Search results

The literature search identified 454 published documents. After a review of their titles and abstracts, 22 studies were retrieved for further evaluation. Of these 22 studies, five full-text articles met the

final inclusion and exclusion criteria. See Figure E.A.1 in Appendix E.A for the progress through the selection of potentially relevant studies.

Evidence from published economic literature

Refer to Table E.A.2 in Appendix E.A for a detailed summary of individual studies included in the review. Scuffham and Carr[7] conducted a simulation model to evaluate the costs and outcomes of IPT compared with MDI for the treatment of type 1 diabetes over an 8-year time frame. The analysis was conducted from the perspective of the UK health care system and used cost data from the British National Formulary and drug tariffs. Cost items included costs of insulin pump, IPT and MDI consumables, insulin, hypoglycemic and ketoacidosis events, and hospitalizations. The results showed that for adults, compared to MDI, IPT was associated with 0.47 additional quality-adjusted life years (QALYs) (7.32 versus 6.85) at an additional cost of CAD 9240[2] (CAD 16,095 versus CAD 6855), producing an incremental cost-effectiveness ratio (ICER) of CAD 19,389 per QALY gained. The authors concluded that IPT is cost-effective when targeted at those who had more than two severe hypoglycemic events per year and required hospital inpatient treatment at least once every 8 months for hypoglycemia.

The remaining four full-text articles were studies based on the CORE Diabetes Model (CDM). The CDM[8,9] simulates the epidemiology of T1DM, including the occurrence of diabetes-related comorbidities such as angina, myocardial infarction, heart failure, stroke, neuropathy, foot ulcer, amputation, renal disease, and eye disease. Based on improvements in glycosylated hemoglobin (A1C) level associated with IPT versus MDI, the model can simulate the differential clinical and health outcomes between IPT and MDI. Clinical and epidemiologic data required for the model are generated from the Diabetes Control and Complications Trial,[10] including associated follow-up studies.[11,12]

Using the core model, Roze et al. (United Kingdom, 2005),[13] Cohen et al. (Australia, 2007),[14] Meaghan et al. (USA, 2009),[15] and Charles et al. (Canada, 2009)[6] applied country-specific cost data to the core model to provide estimates for costs and health outcomes.

Results from the United Kingdom[13] showed that in adults, compared to MDI, IPT was associated with 0.76 additional QALYs over their lifetime (12.03 versus 11.27) at an additional cost of CAD 32,832 (CAD 136,205 versus CAD 103,373), producing an ICER of CAD 43,390 per QALY gained. The authors concluded that IPT is cost-effective given that the ICER is lower than conventional cost-effectiveness thresholds.

In Australia[14] the analysis was conducted for both adult and adolescent populations. The results showed that for adults, compared to MDI, IPT was associated with 0.47 additional QALYs over their lifetime (7.95 versus 7.48) at an additional cost of CAD 32,546 (CAD 115,936 versus CAD 83,390), producing an ICER of CAD 69,661 per QALY gained. For adolescents, compared to MDI, IPT was associated with 0.56 additional QALYs over their lifetime (9.64 versus 9.08) at an additional cost of CAD 39,251 (CAD 139,908 versus CAD 100,657) producing an ICER of CAD 70,144 per QALY gained. The authors concluded that IPT is cost-effective given that the ICER is close to conventional cost-effectiveness thresholds.

[2] The cost in other currencies is converted to Canadian dollars (CAD) using exchange rates released on 31 December 2009 by the Bank of Canada. Readers are referred to Table E.A.2 in Appendix E.A for costs in original currencies.

In the United States[15] the analysis was conducted for both adult and adolescent[3] populations. The results showed that for adults, compared to MDI, IPT was associated with 1.06 additional QALYs over their lifetime (12.85 versus 11.79) at an additional cost of CAD 18,861 (CAD 213,702 versus CAD 194,840), producing an ICER of CAD 17,783 per QALY gained. For adolescents, compared to MDI, IPT was associated with 0.80 additional QALYs (14.42 versus 13.62) at an additional cost of CAD 22,747 (CAD 222,498 versus CAD 199,751), producing an ICER of CAD 28,462 per QALY gained. The authors concluded that IPT is cost-effective, given that the ICER is lower than conventional cost-effectiveness thresholds.

In Canada[6] the results showed that in adults, compared to MDI, IPT was associated with 0.66 additional QALYs over their lifetime (10.03 versus 9.37) at an additional cost of CAD 15,591 (CAD 162,807 versus CAD 147,216), producing an ICER of CAD 23,797 per QALY gained. The authors concluded that IPT is cost-effective given that the ICER is lower than conventional cost-effectiveness thresholds (e.g., CAD 50,000 per QALY gained).

Study limitations

An informal quality assessment was conducted using the criteria adapted from Drummond et al.[1] Overall, the studies satisfied the quality criteria with the exception that costs were not valued credibly in four of the five studies. All of the studies reviewed except for Scuffham et al.[7] were carried out under an identical modeling framework and applied epidemiologic inputs from the Diabetes Control and Complications Trial (DCCT)[10] and subsequent follow-up studies.[11,12] Differences in A1C levels observed in the DCCT study were not observed between IPT and MDI but rather IPT or MDI versus usual care. Consequently, these economic studies have incorrectly applied differences in A1C between MDI and IPT and incorrectly calculated potential cost savings associated with prevented secondary complications (e.g., adverse cardiovascular, ophthalmic, and renal events).

Results from Administrative Database Analysis

All costs are standardized to 2009 Canadian dollars (CAD). Table E.2shows the impact of T1DM on hospital, outpatient, and physician resources, reported separately by each target population. In 2007 for preschool children the average costs per patient for hospital, outpatient, and physician services were CAD 5,181, CAD 1,125, and CAD 172, respectively. For children and adolescents the average costs per patient for hospital, outpatient, and physician services were CAD 8,227, CAD 738 and CAD 188, respectively. For adults the average costs per patient for hospital, outpatient, and physician services were CAD 12,427, CAD 666 and CAD 148, respectively. For pregnant women the average costs per patient for hospital, outpatient, and physician services were CAD 3,793, CAD 833 and CAD 195, respectively.

[3] The cohort of children and young adults in the study had a mean age of 13 years, which corresponds to the target population of children and adolescents (7 to 18 years) defined in the report.

Table E.2: Average costs in Canadian dollars (CAD) per patient for hospital, outpatient, and physician services

Group	Hospitalization	Ambulatory	Physician
Preschool children	5181.23	1124.57	171.69
Adolescents	8226.51	738.22	187.98
Adults	12,426.53	666.08	148.05
Pregnant women	3792.62	833.20	195.05
All groups	8247.14	715.32	149.31

Budget Impact Analysis Results

Unit costs

All costs are standardized to 2009 Canadian dollars. The cost per individual per year for MDI is estimated to be CAD 3962. The cost per patient per year for IPT is estimated to be CAD 8561. Thus, the incremental cost per patient per year associated with switching from MDI to IPT is estimated to be CAD 4700 in the first year and CAD 4600 in the subsequent years (Table E.3).

When excluding consumable items and including only costs of pumps, pump accessories, and patient education and training, the incremental cost per patient switching from MDI to IPT per year was estimated to be CAD 5360 in the first year and CAD 5250 in the subsequent years.

Table E.3: Annual costs in Canadian dollars associated with MDI and IPT

Category	IPT	MDI	Diff
Pump[a]	1650	—	1650
Pump accessories[b]	3600	—	3600
One-time patient education and training[b]	220	110	110
Consumable items			
Pen tips[c]	—	467.20	−467.20
Lancets[d]	173.38	138.70	34.68
Test strips[d]	1259.25	1007.40	251.85
Insulin[c]	1879.02	2348.78	−469.76
Total[f]			
First year	8781.02	4072.08	4708.94
Subsequent years	8561.02	3962.08	4598.94
Total (excluding consumable items)			
First year	5470	110	5360
Subsequent years	5250	0	5250

[a]Data were provided by pump manufacturers. The cost of the pump was annualized over the warranty period of the device (i.e., 4 years).
[b]Personal communication, Allison Husband, Diabetes Clinic, Alberta Children's Hospital.
[c]Costs were based on retail prices and assumed an average of four injections per day for MDI.
[d]Costs were based on retail price and assumed an average of four injections per day for MDI. Costs of consumables were assumed to be 25% more when on using IPT (Allison Husband, Diabetes Clinic, Alberta Children's Hospital, personal communication).

[e]Annual cost of insulin on MDI was derived from a published Canadian economic study.[6] Annual cost of insulin for patients with IPT was assumed to be 20% less than patients on MDI (Allison Husband, Diabetes Clinic, Alberta Children's Hospital, personal communication).
[f]The one-time cost of patient education was included only in the first year of switching from MDI to IPT.

Demand estimates

Table E.4 shows the projected number of IPT users. In total 70 preschool children, 460 children and adolescents, 2547 adults, and 100 pregnant women are projected to switch from MDI to IPT. Between 2009 and 2011, the estimated number of IPT users increases from 483 to 1664.

Table E.4: Projected number of IPT users

Group	Year 1	Year 2	Year 3	Total
Children	11	23	36	70
Adolescents	70	149	241	460
Adults	387	826	1,334	2,547
Pregnant women	15	32	52	100
Total	483	1,030	1,664	3,177

Results of budget impact analysis

Table E.5shows the budget impact over the 3 year time horizon for scenario 1, which considers both costs associated with devices for IPT (i.e., insulin pump, pump accessories, and patient education and training) and consumable items (e.g., test strips and insulin), and scenario 2, which includes only the costs associated with devices for IPT. From calculations based on the eligible number of IPT users shown in Table E.4, the incremental cost associated with IPT compared to MDI for T1DM in scenario 1 is CAD 2.28 million in year 1, CAD 4.69 million in year 2, and CAD 7.61 million in year 3. This represents a total cost of CAD 14.57 million over the 3-year period. In scenario 2, the incremental cost is CAD 2.59 million in year 1, CAD 5.36 million in year 2 and CAD 8.69 million in year 3, representing a total cost of CAD 16.63 million over the 3-year period.

Of the total costs over the 3 years in both scenarios, adults account for 80%. This is followed in magnitude by adolescents at 15%, pregnant women at 3%, and children at 2%.

Note that patients on MDI consume more insulin and insulin pen tips (those on IPT use no pen tips), whereas those on IPT use more test strips and lancets. In total, costs for consumable items are higher for patients on MDI than for those on IPT, which means that switching from MDI to IPT will result in cost savings for these components. The option of excluding consumable items is associated with discounting the savings and therefore budget impact in greater in scenario 2 than in scenario 1.

Table E.5: Annual costs ($ millions CAD)

Group	Year 1	Year 2	Year 3	Total
Scenario 1 (including costs associated with devices and consumable items)				
Children	0.05	0.10	0.17	0.32
Adolescents	0.33	0.68	1.10	2.11
Adults	1.82	3.76	6.10	11.68
Pregnant women	0.07	0.15	0.24	0.46
Total	**2.28**	**4.69**	**7.61**	**14.57**
Scenario 2 (including costs associated with devices only)				
Children	0.06	0.12	0.19	0.36
Adolescents	0.38	0.78	1.26	2.41
Adults	2.08	4.29	6.97	13.34
Pregnant women	0.08	0.17	0.27	0.52
Total	**2.59**	**5.36**	**8.69**	**16.63**

Sensitivity analyses

Table E.6 shows the results of the budget impact analysis with changes to various input parameters. Each input parameter was varied at plus or minus 10%. Given that each parameter is varied using a constant percentage of change, the sensitivity analysis can reveal the parameters that have the greatest impact on the budget impact analysis. Accordingly, Table E.6 shows the rank ordering of the parameters from lowest to highest in terms of the parameters that cause the greatest variation to the budget impact.

The results indicate that the budget impact is most sensitive to the costs of pump accessories and the percentage of adult patients using pump therapy. This is followed by insulin costs of MDI, the cost of the pump, the prevalence of T1DM in the diabetic population, and insulin costs of IPT. Costs of consumables such as lancets and test strips rank at the bottom, which implies that changes in these cost items have a minimal impact on the budget impact. Note that excluding the consumable items (i.e., scenario 2) would not change the rank ordering.

Table E.6: Results from sensitivity analysis

Rank	Parameter	Bound value			Cost (CAD millions)	
		Value used in Main Analysis	Lower Estimate (–10%)	Upper Estimate (+10%)	Lower Estimate	Upper Estimate
Scenario 1						
1	Adult eligibility	5.00%	4.50%	5.50%	13.40	15.74
2	Accessory costs	3600	3240	3960	13.42	15.71
3	Insulin costs, MDI	2349	2114	2584	15.31	13.82
4	Percentage of type 1 over type 2	12.63%	11.36%	13.89%	13.83	15.31
5	Insulin costs, IPT	1879	1691	2067	13.97	15.17

Rank	Parameter	Bound value			Cost (CAD millions)	
		Value used in Main Analysis	Lower Estimate (–10%)	Upper Estimate (+10%)	Lower Estimate	Upper Estimate
6	Pump costs	6598	5938	7257	14.04	15.09
7	Transit rate to IPT (%), year 2	66.00%	59.40%	72.60%	14.09	15.04
8	Transit rate to IPT (%), year 3	100.00%	90.00%	100.00%	13.78	14.57
9	Transit rate to IPT (%), year 1	33.00%	29.70%	36.30%	14.35	14.79
10	Adolescent eligibility	11.70%	10.53%	12.87%	14.36	14.78
11	Prevalence of T1DM in adults	6.60%	5.94%	7.26%	14.40	14.74
12	Pen/syringe price	32.00	28.80	35.20	14.72	14.42
13	Test strips price	69.00	62.10	75.90	14.49	14.65
14	Pregnant eligibility	5.00%	4.50%	5.50%	14.52	14.61
15	Education costs for MDI	110	99	121	14.61	14.53
16	Education costs for IPT	220	198	242	14.53	14.61
17	Children eligibility	11.70%	10.53%	12.87%	14.54	14.60
18	Prevalence of T1DM in adolescents	6.60%	5.94%	7.26%	14.54	14.60
19	Lancet price	9.50	8.55	10.45	14.56	14.58
20	Prevalence of T1DM in pregnant women	6.60%	5.94%	7.26%	14.56	14.58
21	Prevalence of T1DM in children	6.60%	5.94%	7.26%	14.56	14.57
Scenario 2						
1	Adult eligibility	5.00%	4.50%	5.50%	15.30	17.97
2	Accessory costs	3600	3240	3960	15.49	17.78
3	Percentage of type 1 over type 2	12.63%	11.36%	13.89%	15.79	17.48
4	Transit rate to IPT (%), year 2	66.00%	59.40%	72.60%	16.09	17.18
5	Pump costs	6598	5938	7257	16.11	17.16
6	Transit rate to IPT (%), year 3	100.00%	90.00%	100.00%	15.74	16.63
7	Transit rate to IPT (%), year 1	33.00%	29.70%	36.30%	16.39	16.88
8	Adolescent eligibility	11.70%	10.53%	12.87%	16.39	16.88
9	Prevalence of T1DM in adults	6.60%	5.94%	7.26%	16.44	16.83
10	Pregnant eligibility	5.00%	4.50%	5.50%	16.58	16.69
11	Education costs for MDI	110	99	121	16.68	16.59
12	Education costs for IPT	220	198	242	16.60	16.67
13	Children eligibility	11.70%	10.53%	12.87%	16.60	16.67
14	Prevalence of T1DM in adolescents	6.60%	5.94%	7.26%	16.60	16.67
15	Prevalence of T1DM in pregnant	6.60%	5.94%	7.26%	16.63	16.64

Rank	Parameter	Bound value			Cost (CAD millions)	
		Value used in Main Analysis	Lower Estimate (–10%)	Upper Estimate (+10%)	Lower Estimate	Upper Estimate
	women					
16	Prevalence of T1DM in children	6.60%	5.94%	7.26%	16.63	16.64
17	Pen/syringe price	32.00	28.80	35.20	16.63	16.63
17	Lancet price	9.50	8.55	10.45	16.63	16.63
17	Test strips price	69.00	62.10	75.90	16.63	16.63
17	Insulin costs, IPT	1879	1691	2067	16.63	16.63
17	Insulin costs, MDI	2349	2114	2584	16.63	16.63

[a]Costs associated with MDI are inversely related to the budget impact. Therefore, the lower cost estimate appears greater than the upper estimate.

Discussion

The objective of the economic analysis is to inform the economic impact of replacing multiple daily injections with insulin pump therapy for eligible patients with T1DM in Alberta. Specifically, the economic analysis is to inform six questions (refer to section 5.1). A literature review was conducted to inform the cost-effectiveness of IPT compared to MDI for the treatment of T1DM. An analysis of administrative health data was conducted to inform the economic impact of T1DM on physician, hospital, and outpatient services for preschool children, adolescents, adults, and pregnant women. A budget impact analysis was conducted to determine the cost impact of switching from MDI to IPT for eligible preschool children, adolescents, adults, and pregnant women with T1DM in Alberta.

The literature review indicated that compared to MDI, IPT is associated with improved health outcomes (i.e., QALY or life expectancy) but at an additional cost to the health system. In adults the difference in costs ranged between CAD 15,591 and CAD 32,832, whereas the difference in health outcomes ranged between 0.467 QALYs and 1.06 QALYs. In adolescents the difference in costs ranged between CAD 22,747 and CAD 39,251, whereas the difference in health outcomes ranged between 0.56 QALYs and 0.80 QALYs. The cost per additional QALY gained ranged between CAD 28,462 and CAD 70,144. In adults the ICER (i.e., return on investment) ranged between CAD 17,783 and CAD 70,144 per additional QALY gained.

The costs per QALY gained reported in most studies fall below conventional standards of cost-effectiveness (i.e., less than CAD 50,000 per QALY), and the authors conclude that IPT is cost-effective when compared to MDI for the treatment of T1DM. However, in four out of the five studies reviewed, the researchers incorrectly assumed that IPT is associated with better control of A1C levels compared to MDI and incorrectly calculated potential cost savings associated with preventing secondary cardiovascular, ophthalmic, and renal adverse events. Thus, one study[7] provided evidence to inform the cost-effectiveness of IPT compared to MDI but examined only a select group of the adult population. This study indicated that in adults with severe hypoglycemic events requiring inpatient treatment every 8 months, IPT was associated with an ICER of CAD 19,389 per QALY gained compared to MDI. Moreover, none of the studies reviewed included preschool children or pregnant women in their analysis.

Therefore, there is currently limited evidence available in the economic research literature to inform the cost-effectiveness of IPT compared to MDI in preschool children, adolescents, adults, and pregnant women. That is, IPT has not been demonstrated in the published economic literature to be cost-effective compared to MDI. Note that the published economic literature also provided no information regarding whether there is potential for transfer of service and funds from existing services that would be replaced or reduced in usage as well on the impact on the health system of such transfers (policy question 2 in section 5.1).

The analysis of provincial administrative health data indicated that for preschool children, the average cost per patient for hospital, outpatient, and physician services was CAD 5181, CAD 1125, and CAD 172, respectively. For children and adolescents, the average cost per patient for hospital, outpatient, and physician services was CAD 8227, CAD 738, and CAD 188, respectively. For adults the average cost per patient for hospital, outpatient, and physician services was CAD 12,427, CAD 666, and CAD 148, respectively. For pregnant women the average cost per patient for hospital, outpatient, and physician services was CAD 3793, CAD 833, and CAD 195, respectively.

It is important to note that technologies that result in better control of A1C levels may have the potential to generate cost savings in the health system from reducing the risk of secondary complications such as cardiovascular, renal, and ophthalmic adverse events. The currently available evidence (refer to the T section of the report) does not demonstrate a clinically significant difference in A1C reductions between IPT and MDI over a short period (up to 2 years). Therefore, the extent to which one can assume that IPT may minimize secondary complications in patients who switch to IPT from MDI is limited.

Based on the budget impact analysis, the cost per IPT patient per year is estimated to be CAD 4700 in the first year (includes initial patient education and training costs) and CAD 4600 in subsequent years. This cost increases to CAD 5360 and CAD 5250 in the first and subsequent year respectively when excluding consumables. The cost per IPT patient is driven primarily by the cost of the pump device. There are 3177 projected IPT users in Alberta between 2009 and 2011.

In years 1, 2, and 3, the budget impact of IPT is estimated to be CAD 2.28, CAD 4.69, and CAD 7.61 million, respectively. The total budget impact over the 3 year time horizon is CAD 14.57 million. When excluding the consumables, the budget impact estimate is CAD 2.59, CAD 5.36, and CAD 8.69 in years 1, 2, and 3, respectively, representing a total cost of CAD 16.63 million over 3 years. Adults account for 80% of the costs, followed by children and adolescents at 15%, pregnant women at 3%, and preschool children at 2%. It is important to mention that the cost of IPT will continue to increase beyond the 3 year time horizon. Given that T1DM is a chronic condition and that the prevalence of T1DM is projected to increase over time,[16,17] there will likely be a corresponding increase in the demand for IPT. Consequently, the cost of IPT could exceed CAD 7.61 million per year beyond the 3 year time horizon.

The sensitivity analysis indicates that the primary cost driver in the budget impact analysis is the uptake of IPT in the adult population, which represents the largest population of patients with T1DM who could potentially switch from MDI to IPT (i.e., represent the greatest demand). Another significant cost driver was the cost of the pump device, including accessories. This is because the cost per patient per year on IPT is twice that of MDI and the cost of the pump device, including accessories, accounts for 60% of the total cost of IPT per patient per year. The budget was less strongly affected by changes in education costs because education costs accounted for only 2.5% of the total cost of IPT per patient per year. This is an important finding because there may be

variability in the education package and the comprehensiveness of patient support associated with IPT.

Conclusion

From the literature review, analysis of administrative health databases, and budget impact analysis three main points emerge:

1. There is currently limited available evidence in the economic research literature to inform the cost-effectiveness of IPT compared to MDI. That is, IPT has not been demonstrated in the published economic literature to be cost-effective compared to MDI.
2. The economic impact of T1DM, including associated secondary complications on hospital, outpatient, and physician resources, in Alberta is estimated to be CAD 8247, CAD 715, and CAD 149 per patient in 2007 respectively. Long-term evidence is lacking on the impact of IPT on secondary complications.
3. The cost impact of switching from MDI to IPT for eligible patients with T1DM in Alberta is estimated at CAD 14.57 million over 3 years. The cost per IPT user per year is approximately CAD 4,700 in the first year of switching to IPT and CAD 4600 in the subsequent years. When excluding consumables and only considering the costs associated with the insulin pump, the cost per patient per year is estimated to be CAD 5,360 in the first year and CAD 5250 in the subsequent years, indicating a total budget impact of CAD 16.63 million over 3 years. Adults account for 80% of the costs, followed by adolescents at 15%, pregnant women at 3%, and children at 2%.

Caveats

It is important to evaluate the analysis in light of the following caveats:

1. Limitations in Alberta-specific epidemiologic data and timelines prevented a primary cost-effectiveness analysis contextualized to Alberta. Cost-effectiveness was therefore addressed using evidence from the published literature. The extent to which the results from the published literature can be generalized to the Alberta context is unknown due to local differences in clinical practice, epidemiology, and costs (note that all but one study used the same diabetic model[8,9] in their analysis). Furthermore, four out of the five studies reviewed incorrectly applied clinical information in their cost analysis, leaving only one study to inform the cost-effectiveness of IPT compared to MDI. Furthermore, this study included only a highly select group of adult patients with severe hypoglycemia. Thus, the cost-effectiveness of IPT compared to MDI for the treatment of T1DM for preschool children, adolescents, adults, and pregnant women in Alberta remains unknown.
2. Identifying T1DM in the Alberta population for the budget impact analysis was based on using diagnostic coding information contained in the provincial administrative health databases. There are two primary limitations with this approach. First, the service event data contained in the physician claims database does not differentiate between type 1 and type 2 diabetes. Type 1 diabetes was differentiated from type 2 diabetes using estimates generated from the Canadian Community Health Survey. Second, although the diagnostic coding information contained in the inpatient database does differentiate type 1 from type 2 diabetes, it might be skewed toward a higher proportion of type 1 diabetes patients. These two limitations introduce uncertainty regarding the accuracy of the prevalence estimates for T1DM in Alberta. Nevertheless, using billing data to estimate the prevalence of diabetes has

been used in the published research literature, and the estimate of the prevalence of T1DM is similar to estimates reported in other provincial reports.[18]

3. The budget impact analysis assumed that one-third of eligible patients will transition to IPT in years 1, 2, and 3, respectively. However, the actual proportion of eligible T1DM patients who will make that transition to IPT in Year 1, 2, and 3 is unknown. On the other hand, the sensitivity analysis indicated that the transition rates were not the major drivers to the budget impact analysis.
4. The budget impact analysis informs only the cost of implementing IPT in Alberta. It does not consider the impact on health outcomes. Thus, the budget impact analysis does not inform whether IPT provides good value for money because it focuses only on costs and does not account for returns on investment in terms of health outcomes (i.e., cost-effectiveness).
5. The budget impact analysis calculates the cost of implementing IPT over a 3-year time horizon. Thus, cost increases or decreases associated with IPT beyond this period are not considered.
6. Program-specific data related to the IPT initiatives in Alberta (e.g., education and training costs, IPT uptake in the target population) were based on personal communication with clinician experts and program managers. Thus, the accuracy the data inputs related to the IPT program and the generalizability across the province is uncertain. A sensitivity analysis was conducted to determine the robustness of the budget impact estimate to varying assumptions. This did indicate that the budget impact is sensitive to the rate of IPT uptake in the adult target population.
7. Provincial administrative health data were used to calculate the resource impact on inpatient, outpatient, and physician services associated with T1DM. However, this raises concerns regarding the accuracy of the cost analysis due to the issues regarding the prevalence estimate of T1DM, stated in caveat 2 above. However as previously noted, the prevalence estimate of T1DM is similar to estimates reported in other provincial reports.

Summary

The objective of the economic analysis is to inform the economic impact of replacing multiple daily injections with insulin pump therapy for eligible patients with T1DM in Alberta. A literature review was conducted to inform the cost-effectiveness of IPT compared to MDI for the treatment of T1DM. An analysis of administrative health data was conducted to inform the economic impact of T1DM on physician, hospital, and outpatient services for preschool children, adolescents, adults, and pregnant women. A budget impact analysis was conducted to determine the cost impact of IPT for preschool children, adolescents, adults, and pregnant women with T1DM in Alberta.

Five studies met the final inclusion criteria for the literature review. However, a review of the studies identified that four incorrectly applied clinical information in their cost analysis. Therefore, only one study provided evidence to inform the cost-effectiveness of IPT compared to MDI but only in a highly select group of adult patients with severe hypoglycemia. The results from this study indicated that compared to MDI, the cost per additional quality-adjusted life year gained (QALY) was GBP 11,461. The authors concluded that IPT is cost-effective when targeted at those who had more than two severe hypoglycemic events per year and required hospital inpatient treatment at least once every 8 months for hypoglycemia.

Technologies that result in better control of A1C levels have the potential to generate cost savings in the health system from reducing the risk of associated secondary complications such as cardiovascular, renal, and ophthalmic adverse events. The analysis of administrative health data indicated that in 2007 the health service utilization costs associated with T1DM for children, adolescents, adults, and pregnant women were as follows:

- Hospital costs
  - Preschool children – CAD 5181
  - Adolescents – CAD 8227
  - Adults – CAD 12,427
  - Pregnant women – CAD 3793
  - All groups – CAD 8247
- Outpatient costs
  - Preschool children – CAD 1125
  - Adolescents – CAD 738
  - Adults – CAD 666
  - Pregnant women – CAD 833
  - All groups – CAD 715
- Physician costs
  - Preschool children – CAD 172
  - Adolescents – CAD 188
  - Adults – CAD 148
  - Pregnant women – CAD 195
  - All groups – CAD 149

The currently available evidence (refer to the T section of the report) does not demonstrate a clinically significant difference in A1C reductions between IPT and MDI over a short period (up to 2 years). Therefore, the extent to which one can assume that IPT will minimize secondary complications in patients who switch to IPT from MDI is limited.

The budget impact analysis was conducted over a 3 year time horizon, and the estimated incremental cost per patient per year is CAD 4700 in the first year (first year includes costs of initial patient education and training) and CAD 4600 in the subsequent years. There are 3177 projected eligible IPT users in Alberta between 2009 and 2011. Assuming that approximately a third of the eligible target population will transition to IPT each year, the budget impact of IPT is estimated to be CAD 2.28, CAD 4.69, and CAD 7.61 million in 2009, 2010, and 2011, respectively. The total budget impact of IPT over 3 years is estimated at CAD 14.57 million. Of the total budget impact, adults account for 80% of the costs, followed by 15% for children and adolescents, 3% for pregnant women, and 2% for preschool children.

When excluding consumable items and including only the costs of the pump, pump accessories, and initial patient education and training, the cost per patient on IPT per year was estimated to be CAD

5360 in the first year and CAD 5250 in the subsequent years. Note that costs for consumable items are higher for patients on MDI than for those on IPT, which means that switching from MDI to IPT will also result in cost savings for these components. The option of excluding consumable items is associated with discounting the savings. The budget impact estimates increase to CAD 2.59, CAD 5.36, and CAD 8.69 million in 2009, 2010, and 2011, respectively. The total budget impact of IPT over 3 years is estimated at CAD 16.63 million. Therefore, the budget impact is greater in the scenario where consumable items are excluded. Of the total budget impact, adults account for 80% of the costs, followed by 15% for children and adolescents, 3% for pregnant women, and 2% for preschool children.

It is important to note that the cost of IPT will continue to increase beyond the 3 year time horizon because T1DM is a chronic condition and the prevalence of T1DM is projected to increase over time, resulting in an increase in the demand for IPT. Consequently, the cost of IPT could exceed CAD 7.61 million per year beyond the 3 year time horizon.

Based on the literature review, analysis of administrative health databases, and budget impact analysis, three main points emerge:

1. There is currently limited available evidence in the economic research literature to inform the cost-effectiveness of IPT compared to MDI. That is, IPT has not been demonstrated in the published economic literature to be cost-effective compared to MDI.
2. The impact of T1DM, including associated secondary complications, on hospital, outpatient, and physician resources in Alberta, is estimated to be CAD 8247, CAD 715, and CAD 149 per patient in 2007, respectively. Long-term evidence is lacking on the impact of IPT on secondary complications.
3. The cost impact of switching from MDI to IPT for eligible patients with T1DM in Alberta is estimated at CAD 14.57 million over 3 years. The cost per IPT user per year is approximately CAD 4700 in the first year of switching to IPT and CAD 4600 in the subsequent years. When excluding consumables and considering only the costs associated with the insulin pump, the cost per patient per year is estimated to be CAD 5360 in the first year and CAD 5250 in the subsequent years, indicating a total budget impact of CAD 16.63 million over 3 years. Adults account for 80% of the costs, followed by adolescents at 15%, pregnant women at 3%, and children at 2%.

APPENDICES

Appendix E.A: Literature Search Summary

General Information

The search strategy outlined below retrieved articles published from 1999 to June 2009. The search was designed to retrieve economic evaluations of insulin pump therapy.

Medical Subject Headings (MeSH) terms relevant to this topic are Insulin Infusion Systems; Diabetes Mellitus, Type 1; Costs and Cost Analysis; and Cost-Benefit Analysis

Table E.A.1: Search strategies

Database	Edition or date searched	Search terms[a]
Core databases		
The Cochrane Library http://www.thecochranelibrary.com	19 June 2009	"continuous or pump* or infusion* or IPT or CSII or injection* or MDI in Title, Abstract or Keywords and insulin in Title, Abstract or Keywords and diabet* in Title, Abstract or Keywords and cost* or economic* or financ* or budget* or pharmacoeconomic* in Title, Abstract or Keywords, from 1999 to 2009
MEDLINE (OVID interface)	19 June 2009	1 Insulin Infusion Systems/ 2 infusion pumps/ or infusion pumps, implantable/ 3 (insulin or novorapid or humalog or apidra or humulin$ or novolin or levemir or lantus).mp. 4 exp Infusions, Parenteral/ 5 3 and (2 or 4) 6 Administration, Cutaneous/ 7 exp Injections/ 8 exp Insulin/ 9 (6 or 7) and (3 or 8) 10 (insulin pump$ or insulin infusion$ or CSII).mp. 11 (subcutaneous adj2 insulin).mp. 12 (continuous adj2 insulin).mp. 13 ((closed-loop adj2 control) and (insulin or glucose)).mp. 14 (multiple daily injection$ or MDI).mp. 15 1 or 5 or 9 or 10 or 11 or 12 or 13 or 14 16 exp Diabetes Mellitus, Type 1/

MEDLINE (OVID interface) (cont'd)	19 June 2009	17 diabet$.mp. 18 diabetes mellitus/ or diabetes, gestational/ 19 (T1DM or IDDM).mp. 20 or/16-19 21 (type 2 not (type 1 and type 2)).mp. 22 20 not 21 23 15 and 22 24 exp Diabetes Complications/ 25 exp Economics/ 26 "Costs and Cost Analysis"/ 27 Cost-Benefit Analysis/ 28 "cost of illness"/ 29 (economic evaluat$ or economic analys$ or economic study or economic studies or economic assess$ or economic consequence$).mp. 30 ((cost-benefit or benefit-cost or cost effectiv$ or cost utility) adj2 (analys$ or evaluat$ or assess$ or study or studies or ratio$)).mp. 31 (cost minimization or cost minimisation or cost consequence$ or cost offset$).mp. 32 ((cost or costs) adj2 analys$).mp. 33 ("cost of illness" adj4 (analys$ or evaluat$ or assess$ or study or studies or framework$)).mp. 34 cost of illness.ti. 35 cost implication$.mp. 36 (cost$ or economic$ or budget$ or pharmacoeconomic$ or financ$).mp. 37 ec.fs. 38 or/25-37 39 employment/ or employment, supported/ or unemployment/ 40 absenteeism/ or efficiency/ or exp "task performance and analysis"/ 41 disability evaluation/ or work capacity evaluation/ 42 (employment or unemploy$ or productivity or absentee$ or disability).mp. 43 or/39-42 44 (23 or (15 and 24)) and (38 or 43) 45 humans/ 46 animals/ 47 46 not (45 and 46)

		48 44 not 47 49 limit 48 to yr="1999-Current" 50 ((longterm or long-term) adj2 (impact or effect$)).mp. 51 23 and 50 52 51 not 47 53 limit 52 to yr="1999-Current" 54 49 or 53
EMBASE (OVID interface)	19 June 2009	1 insulin pump/ 2 infusion system/ or infusion pump/ or continuous infusion/ 3 insulin infusion/ 4 exp insulin treatment/ and (injection$ or pump$).mp. 5 Subcutaneous Drug Administration/ 6 exp Injection/ 7 (insulin or novorapid or humalog or apidra or humulin$ or novolin or levemir or lantus).mp. 8 (2 or 5 or 6) and 7 9 (subcutaneous adj2 insulin).mp. 10 (continuous adj2 insulin).mp. 11 (insulin pump$ or insulin infusion$ or CSII).mp. 12 ((closed-loop adj2 control) and (insulin or glucose)).mp. 13 (multiple daily injection$ or mdi).mp. 14 1 or 3 or 4 or 8 or 9 or 10 or 11 or 12 or 13 15 exp Diabetes Mellitus/ 16 (diabet$ or T1DM or IDDM).mp. 17 15 or 16 18 14 and 17 19 (Type 2 not (type 1 and type 2)).ti,ab. 20 18 not 19 21 health economics/ or exp economic evaluation/ or exp "health care cost"/ or pharmacoeconomics/ or "drug cost"/ 22 economic evaluation/ or "cost benefit analysis"/ or "cost effectiveness analysis"/ or "cost minimization analysis"/ or "cost utility analysis"/ 23 "cost of illness"/ 24 (economic evaluat$ or economic analys$ or economic study or economic studies or economic assess$ or economic consequence$).mp. 25 ((cost-benefit or benefit-cost or cost effectiv$ or cost utili$) adj2 (analys$ or evaluat$ or assess$ or study or studies or

		ratio$)).mp. 26 (cost minimization or cost minimisation or cost consequence$ or cost offset$).mp. 27 ((cost or costs) adj2 analys$).mp. 28 ("cost of illness" adj4 (analys$ or evaluat$ or assess$ or study or studies or framework$)).mp. 29 cost of illness.ti. 30 cost implication$.mp. 31 (cost$ or economic$ or budget$ or pharmacoeconomic$ or financ$).ti. 32 or/21-31 33 20 and 32 34 (exp vertebrate/ or animal/ or exp experimental animal/ or nonhuman/ or animal.hw.) not (exp human/ or human experiment/) 35 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. not (exp human/ or human experiment/) 36 34 or 35 37 33 not 36 38 exp employment/ 39 absenteeism/ or job performance/ or productivity/ or work capacity/ or workload/ or work schedule/ 40 Disability/ 41 (employment or unemploy$ or productivity or absentee$ or disability).mp. 42 or/38-41 43 20 and 42 44 37 or 43 45 limit 44 to yr="1999-Current"
CRD Databases (DARE, HTA & NHS EED)	19 June 2009	# 1 MeSH Insulin Infusion Systems # 2 MeSH Infusion Pumps EXPLODE 1 2 # 3 MeSH Infusions, Parenteral EXPLODE 1 # 4 MeSH Administration, Cutaneous # 5 MeSH Insulin EXPLODE 1 2 # 6 insulin OR novorapid OR humalog OR apidra OR humulin* OR novolin OR levemir OR lantus # 7 #2 OR #3 OR #4 # 8 #5 OR #6

		# 9 #7 AND #8 # 10 "insulin pump" OR "insulin pumps" OR "insulin infusion" OR "insulin infusions" OR CSII OR "continuous insulin" OR "continuous subcutaneous" OR IPT # 11 #1 OR #9 OR #10 # 12 MeSH Injections EXPLODE 1 # 13 #12 and #8 # 14 "multiple daily injection" OR "multiple daily injections" OR MDI # 15 #11 OR #13 OR #14 # 16 diabetes # 17 MeSH Diabetes Mellitus EXPLODE 1 2 # 18 #16 OR #17 # 19 #15 AND #18 # 20 #19 RESTRICT YR 1999 2009 # 21 MeSH Economics EXPLODE 2 # 22 cost* OR economic* OR budget* OR financ* OR pharmacoeconomic* # 23 #21 OR #22 # 24 #20 AND #23
CINAHL	19 June 2009	**1.** (((MH "Infusion Pumps+") OR (MH "Infusions, Subcutaneous")) and ((MH "Insulin+") OR (insulin or novorapid or humalog or apidra or humulin$ or novolin or levemir or lantus))) or ("continuous insulin" or "continuous subcutaneous" or "insulin pump*" or "insulin infusion*" or IPT or CSII) or ("multiple daily injection*" or MDI) 2. (MH "Diabetes Mellitus, Insulin-Dependent") OR (MH "Diabetes Mellitus") OR (MH "Pregnancy in Diabetes+") OR diabet* 3. 1 AND 2 4. ((MH "Costs and Cost Analysis+")) or (cost* or economic* or budget* or financ* or pharmacoeconomic*) or (MH "Economic Aspects of Illness") 5. 3 and 4
Web of Science	19 June 2009	Topic=("insulin pump*" or "insulin infusion*" or CSII or IPT or "subcutaneous insulin" or "multiple daily injection*" or MDI) AND Topic=(insulin AND diabet*) AND Topic=(cost* or economic* or budget* or financ* or pharmacoeconomic*) Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=1999-2009

Biosis Previews	19 June 2009	Topic=("insulin pump*" or "insulin infusion*" or CSII or IPT or "subcutaneous insulin" or "multiple daily injection*" or MDI) AND Topic=(cost* or economic* or budget* or financ* or pharmacoeconomic*) AND Topic=(insulin AND diabet*) Databases=PREVIEWS Timespan=1999-2009
EconLit	19 June 2009	("insulin pump*" or "insulin infusion*" or CSII or IPT or "subcutaneous insulin" or "multiple daily injection*" or MDI) AND (cost* or economic* or budget* or financ* or pharmacoeconomic*) AND diabet* Only 1 result retrieved. Was a duplicate, so file not saved.
PubMed	19 June 2009	#6 Search #1 AND #2 AND #3 AND #4 Limits: Publication Date from 1999 to 2009 #5 Search #1 AND #2 AND #3 AND #4 #4 Search cost* or economic* or budget* or financ* or pharmacoeconomic* #3 Search in process[sb] OR pubmednotmedline[sb] OR publisher[sb] #2 Search diabet* #1 Search insulin pump* OR insulin infusion* OR CSII OR IPT OR subcutaneous insulin OR MDI or multiple daily injection*
Health Economics Resources		
Centre for Health Economics and Policy Analysis http://www.chepa.org	10 February 2009	insulin
Centre for Health Economics Research and Evaluation http://datasearch.uts.edu.au/chere/research/SearchPublication.cfm	10 February 2009	insulin
Library catalogues		
NEOS catalogue	10 February 2009	"insulin pump"; "insulin pumps"; "insulin infusion"; "insulin infusions"; CSII
Websites		
Canadian Diabetes Association (http://www.diabetes.ca/)	4 March 2009	

[a] "*", "#", and "?" are truncation characters that retrieve all possible suffix variations of the root word; e.g., surg* retrieves surgery, surgical, surgeon, etc.

Searches separated by semicolons have been entered separately into the search interface.

Figure E.A.1: Progress through selection of potentially relevant studies

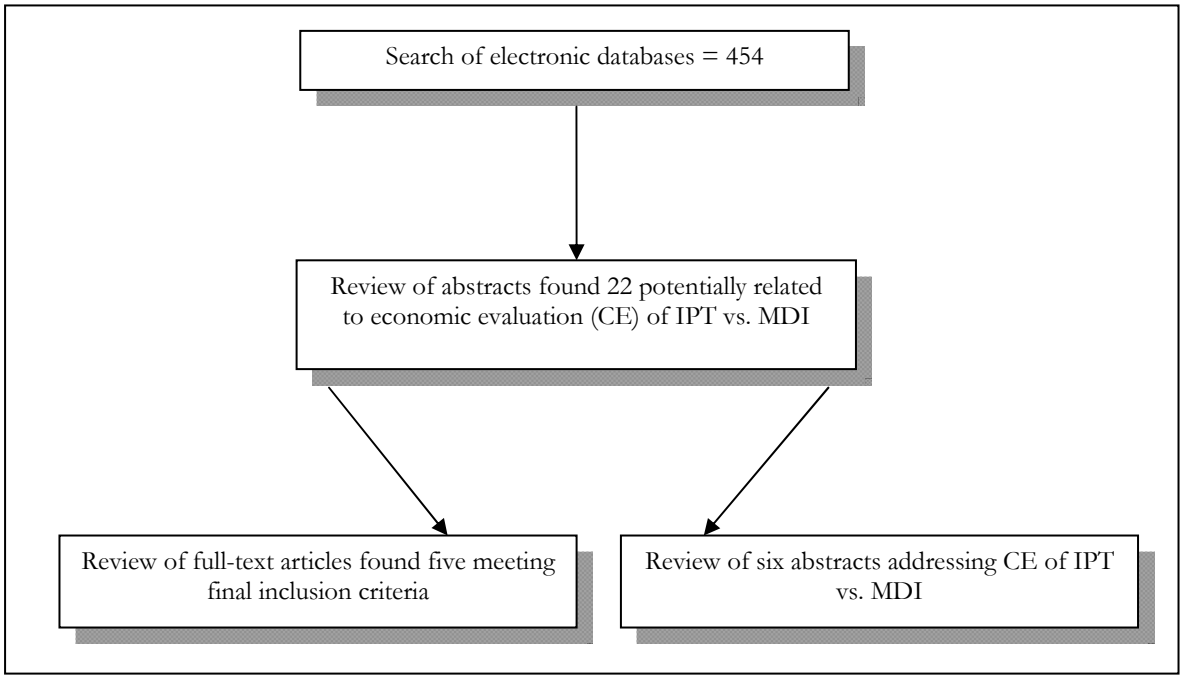

Table E.A.2: Summary of primary studies of the cost impact

Author/Country	Study Type	Objective / Perspective	Study Population	Health Outcome	Timeline/ Cost Year	Results	Study Conclusions
Cohen/ 2007[14] Australia	CEA, CUA	To estimate long-term costs and outcomes of IPT compared with MDI/Australian single-payer health care system	Adult: mean age 43 yrs with 8.2 Adolescent: mean age 17 yrs with 9.8	LE QALYs	Lifetime/ 2006 AUD	For adults, IPT vs. MDI produce an ICER of AUD 88,220 per life yr gained and AUD 74,147 per QALY gained (QALYs: 7.95 vs. 7.483; LE: 11.707 vs. 11.315 yrs; and lifetime costs: AUD 123,402 vs. 88,760) For adolescents, IPT vs. MDI produces an ICER of AUD 77,851 per life yr gained and AUD 74, 661 per QALY gained (QALYs: 9.642 vs. 9.082; LE: 14.224 vs. 13.708 yrs; and lifetime costs: AUD 148, 918 vs. 107,139)	IPT leads to improvement in LE and QALY for adults and adolescents with T1DM. IPT produces ICERs that are very close to the threshold representing good value for money.
Roze 2005[13] United Kingdom	CEA, CUA	To evaluate costs and outcomes of using IPT compared with MDI / UK NHS	Adult: mean age 26 yrs with 8.68	LE QALY	Lifetime/ 2003 GBP	IPT vs. MDI produce an ICER of GBP 27,477 per LE gained and GBP 25,648 per QALY gained (QALYs: 12.03 vs. 11.27; LE: 17.44 vs. 16.73 yrs; and lifetime costs: GBP 80,511 vs. GBP 61,104)	IPT leads to improved QALYs for adults with T1DM. The ICER is within the range considered good value for money in the UK.
Scuffham 2003[7] United Kingdom	CUA	To evaluate costs and outcomes of IPT compared with MDI. / UK NHS	UK T1DM patients; not reporting age and level	QALY	8 yrs/ 2001 GBP	IPT vs. MDI produce an ICER of GBP 11,461 per QALY gained (QALYs: 7.32 vs. 6.85; and costs per patient: GBP 9514 vs. GBP 4052)	IPT is a worthwhile investment when targeted at those who had more than two severe hypoglycemic events per year and required hospital inpatient treatment at least once every 8 months for hypoglycemia.

Meaghan 2009[15] United States	CEA, CUA	To estimate long-term costs and outcomes of IPT compared with MDI / third-party payer	Adult: mean age 27 yrs with 8.95 Adolescent: mean age 13 yrs with 8.2	LE QALY	60 yrs/2007 USD	For adults, IPT vs. MDI produce an ICER of USD 18,268 per life yr gained and USD 16,992 per QALY gained (QALYs: 12.848 vs. 11.788; LE: 18.874 vs. 17.888 yrs; and costs: USD 204,192 vs. 186,170) For adolescents, IPT vs. MDI produces an ICER of USD 31,259 per LE gained and USD 27,195 per QALY gained (QALYs: 14.418 vs. 13.618; LE: 20.827 vs. 20.132 yrs; and lifetime costs: USD 212,597 vs. 190,862)	IPT is a cost-effective treatment for patients with T1DM, given a threshold of USD 50,000 per QALY gained.
St. Charles 2009[6] Canada	CEA, CUA	To estimate long-term costs and outcomes of IPT compared with MDI / provincial government	Adult: mean age 27 yrs with 8.95	LE QALY	60 yrs/2006 CAD	IPT vs. MDI produce an ICER of CAD 27,264 per LE gained and CAD 23,797 per QALY gained (QALYs: 10.029 vs. 9.374; LE: 14.562 vs. 13.990 yrs; and lifetime costs: CAD 162,807 vs. CAD 147,216)	IPT is a cost-effective treatment for Canadian adults with T1DM.

[a]Abbreviations: AUD = Australian dollar; CEA=cost-effectiveness analysis; CUA=cost-utility analysis; GBP = Great Britain pound; ICER = incremental cost-effectiveness ratio; LE = life expectancy; MDI = multiple daily injections; NHS = National Health Service; QALY = quality-adjusted life year; T1DM = type 1 diabetes mellitus; USD = United States dollars; yr = year

Appendix E.B: Calculation of eligible IPT users and costs

Table E.B.1: STEs of estimating IPT users

STE	Group/Type	Number of patients identified in each fiscal year			Description
		2006	2007	2008	
1. Identifying patients	*Children (0 to 6 yrs)*				Diabetes patients not being identified are labeled as "type 1 or 2". Data source: AHW administrative datasets
	Type 1	233	220	236	
	Type 1 or 2	181	208	170	
	Adolescents (7 to 18)				
	Type 1	1576	1504	1625	
	Type 1 or 2	497	579	595	
	Adults (19+)				
	Type 1	7470	9037	8824	
	Type 1 or 2	93,529	98,171	104,527	
	Pregnant women				
	Type 1	164	361	372	
	Type 1 or 2	2458	3002	3904	
2. Estimating number of patients with T1DM	**Group**	**2006**	**2007**	**2008**	Assumption is based on CCHS: 12.63% of diabetes patients are with type 1. Summing the proportion of type 1 patients in STE 1 provides an estimate of patients with type 1 diabetes.
	Children	256	246	258	
	Adolescents	1639	1577	1700	
	Adults	19,279	21,432	22,022	
	Pregnant women	474	740	865	
	Total	**21,648**	**23,996**	**24,845**	
3. Estimating the trend in T1DM development	**Group**	**2006 vs. 2007**	**2007 vs. 2008**	**Mean value**	The number of patients calculated in STE 2 is used to calculate the rate of change over time.
	Children	–4%	4%	0.24%	
	Adolescents	–4%	7%	1.66%	
	Adults	10%	3%	6.36%	
	Pregnant women	36%	14%	25.17%	
	Total	**10%**	**3%**	**6.60%**	

4. Projecting the number of patients with T1DM	**Group**	**2009**	**2010**	**2011**	The average rate of change (6.6%) calculated in STE 3 is used to estimate the number of patients with T1DM in following years.
	Children	275	293	312	
	Adolescents	1812	1932	2059	
	Adults	23,475	25,025	26,676	
	Pregnant women	922	983	1048	
	Total	**275**	**293**	**312**	
5. Projecting number of eligible IPT users	**Group**	**2009**	**2010**	**2011**	It is assumed that 5% of adults/pregnant women and 11.7% of children/adolescents are eligible for IPT.
	Children	32	34	36	
	Adolescents	212	226	241	
	Adults	1174	1251	1334	
	Pregnant women	46	49	52	
	Total	**1464**	**1561**	**1664**	
6. Projecting number of eligible users transition to IPT	**Group**	**2009**	**2010**	**2011**	The transition rate was assumed to be one-third each year. "New" indicates patients using the pump in the 1st year. "Old" indicates those using pump in the subsequent years.
	Children: new	11	12	14	
	Children: old	—	11	23	
	Adolescents: new	70	79	92	
	Adolescents: old	—	70	149	
	Adults: new	387	438	508	
	Adults: old	—	387	826	
	Pregnant women: new	15	17	20	
	Pregnant women: old	—	15	32	
	Total	**483**	**1030**	**1664**	

[a]Abbreviations: CCHS=Canadian Community Health Survey; IPT = insulin pump therapy; T1DM = type 1 diabetes mellitus

References

1. Drummond MF, Sculpher MJ, Torrance GW, et al. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford, UK: Oxford University Press; 2005.
2. National Diabetes Surveillance System (NDSS). *National Diabetes Surveillance System Methods Documentation, 2008*. [cited 2009 Apr 29]. Available from: *http://www.phac-aspc.gc.ca/ccdpc-cpcmc/ndss-snsd/english/diabetes_data/00-06/pdf/method_v208-eng.pdf*.
3. Patented Medicine Prices Review Board. *Budget impact analysis guidelines*. Patented Medicine Prices Review Board; 2007 May. Report No. H79-1/2007. Available from: *http://www.pmprb-cepmb.gc.ca/cmfiles/bia-may0738lvv-5282007-5906.pdf*.
4. Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N. Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. *Health Technology Assessment* (Winchester, UK) 2004;8(43):iii-171.
5. Hanas R. Selection for and initiation of continuous subcutaneous insulin infusion: proceedings from a workshop. *Hormone Research* 2002;57(Suppl 1):101-4.
6. St. Charles ME, Sadri H, Minshall ME, Tunis SL. Health economic comparison between continuous subcutaneous insulin infusion and multiple daily injections of insulin for the treatment of adult type 1 diabetes in Canada. *Clinical Therapeutics* 2009;31(3):657-67.
7. Scuffham P, Carr L. The cost-effectiveness of continuous subcutaneous insulin infusion compared with multiple daily injections for the management of diabetes. *Diabetic Medicine* 2003;20(7):586-93.
8. Palmer AJ, Roze S, Valentine WJ, et al. Validation of the CORE diabetes model against epidemiological and clinical studies. *Current Medical Research and Opinion* 2004;20(Suppl 1):S27-S40.
9. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, et al. The CORE diabetes model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Current Medical Research and Opinion* 2004;20(Suppl 1):S5-26.
10. 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 England Journal of Medicine* 1993;329(14):977-86.
11. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *New England Journal of Medicine* 2000;342(6):381-9.
12. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *New England Journal of Medicine* 2005;353(25):2643-53.
13. Roze S, Valentine WJ, Zakrzewska KE, Palmer AJ. Health-economic comparison of continuous subcutaneous insulin infusion with multiple daily injection for the treatment of Type 1 diabetes in the UK. *Diabetic Medicine* 2005;22(9):1239-45.

14. Cohen N, Minshall ME, Sharon-Nash L, et al. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin: economic comparison in adult and adolescent type 1 diabetes mellitus in Australia. *Pharmacoeconomics* 2007;25(10):881-97.

15. Meaghan SC, Peter L, Claudia G, et al. Minshall ME. A cost-effectiveness analysis of continuous subcutaneous insulin injection versus multiple daily injections in type 1 diabetes patients: a third-party US payer perspective. *Value in Health* 2009;12:674-86.

16. Canadian Diabetes Association. *The prevalence and costs of diabetes,* 2009 [cited 2009 Oct]. Available from: *http://www.diabetes.ca/about-diabetes/what/prevalence/*.

17. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21(9):1414-31.

18. Johnson JA. *Alberta Diabetes Atlas 2007*. Edmonton, AB: Institute of Health Economics; 2007.

Author Contribution Statements

Paula Corabian contributed to study conception and design, data analysis and interpretation, manuscript preparation, revision of manuscript for critical content, and approved the final version for publication.

Bing Guo contributed to study conception and design, data analysis and interpretation, manuscript preparation, and approved the final version for publication.

Christa Harstall contributed to study conception and design, revision of manuscript for critical content, and approved the final version for publication.

Anderson Chuck contributed to study conception and design, statistical analysis, data analysis and interpretation, revision of manuscript for critical content, and approved the final version for publication.

Charles Yan contributed to study conception and design, statistical analysis, data analysis and interpretation, manuscript preparation, and approved the final version for publication.

This report examines the research evidence on the safety and efficacy of insulin pump therapy, as compared to multiple daily insulin injections, in the treatment of children, adults, and pregnant women diagnosed with type 1 diabetes. The report also analyses the economic impact of introducing the insulin pump therapy in Alberta.

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