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Current Practice Analysis of Health Care Providers and Patients: Second-line Therapy for Patients With Type 2 Diabetes Inadequately Controlled on Metformin

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH) through its Canadian Optimal Medication Prescribing and Utilization Service (COMPUS).

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ABBREVIATIONS

A1C	glycosylated hemoglobin
CAC	COMPUS Advisory Committee
CADTH	Canadian Agency for Drugs and Technologies in Health
CDA	Canadian Diabetes Association
CERC	COMPUS Expert Review Committee
CME	Continuing Medical Education sessions
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
GP	General Practitioner
SMBG	self-monitoring of blood glucose
TZD	thiazolidinediones

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1 INTRODUCTION

In March 2004, the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) — now the Canadian Agency for Drugs and Technologies in Health (CADTH) — launched the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) as a service to federal, provincial, and territorial jurisdictions and other stakeholders. COMPUS is a nationally coordinated program, funded by Health Canada.

The goal of CADTH's COMPUS program is to optimize drug-related health outcomes and cost-effective use of drugs by identifying and promoting optimal drug prescribing and use. Where possible, COMPUS builds on existing applicable Canadian and international initiatives and research. COMPUS goals are achieved through three main approaches:

- identifying evidence-based optimal therapy in prescribing and use of specific drugs
- identifying gaps between clinical practice, then proposing evidence-based interventions to address these gaps
- supporting the implementation of these interventions.

Direction and advice are provided to CADTH through various channels, including the following:

- the COMPUS Advisory Committee (CAC) includes representatives from the federal, provincial, and territorial Health Ministries and related health organizations.
- the COMPUS Expert Review Committee (CERC) members are listed previously in this document. The mandate of CERC is advisory in nature and is to provide recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal drug prescribing and use in Canada.
- stakeholder feedback.

1.1 CERC

CERC consists of eight Core Members appointed to serve for all topics under consideration during their term of office, and three or more Specialist Experts appointed to provide their expertise in recommending optimal therapy for one or more specific topics. For topics in the area of diabetes management, including insulin analogue therapy, blood glucose test strips, and second-line therapy for patients with type 2 diabetes in whom metformin monotherapy has failed, four endocrinologists/ diabetes specialists were appointed as Specialist Experts. Two of the Core Members are Public Members who bring a lay perspective to the committee. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists, or have other relevant qualifications, with expertise in one or more areas such as, but not limited to, family practice, internal medicine, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization expertise, methodology, affecting behaviour change (through health professional and/or patient and/or policy interventions), and critical appraisal. The Core Members including Public Members are appointed by the CADTH Board of Directors.

The mandate of CERC is advisory in nature and consists of providing recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada. The overall perspective used by CERC members in producing recommendations is that of public health care policy-makers in pursuit of optimizing the health of Canadians within available health care system resources.

2 ISSUE

CAC has identified management of diabetes mellitus as being a priority area for optimal practice initiatives based on the following criteria:

- large deviations from optimal utilization (overuse or underuse)
- size of patient populations
- impact on health outcomes and cost-effectiveness
- benefit to multiple jurisdictions
- measurable outcomes
- potential to effect change in prescribing and use.

Within diabetes mellitus management, second-line therapy for patients with type 2 diabetes not adequately controlled on metformin monotherapy was identified by CAC as a priority topic.

Treatment of patients with type 2 diabetes mellitus usually begins with lifestyle modification and treatment with oral antidiabetes drugs. Metformin is recommended as the first-line oral antidiabetes drug in most patients with type 2 diabetes when glycemic control cannot be achieved by lifestyle interventions alone.[1-5] Recent utilization data indicate that approximately 60% of patients with type 2 diabetes mellitus initiating pharmacotherapy in Canada are started on metformin.[6] As type 2 diabetes is a progressive disease, glycemic levels are likely to worsen over time. Most patients eventually require two or more oral antidiabetes drugs, or the addition of an insulin regimen, to achieve or maintain target blood glucose levels.[7,8] Existing guidelines[1-3,9-11] recommend several options for second-line therapy when metformin alone is no longer effective. However, guidelines generally lack specific recommendations regarding which agent(s) are optimal as second-line therapy for patients with type 2 diabetes mellitus not adequately controlled with metformin monotherapy. Rather, a general recommendation that a stepwise approach be used to add agents from various classes is often provided. Guideline recommendations in this area are based primarily on evidence regarding clinical efficacy and safety; cost-effectiveness is often not considered.

Canadians spent approximately $17.10 per capita on oral diabetes drugs in 2007, for a total of $563 million.[12] The average cost per oral antidiabetes drug prescription in publicly funded drug plans in Canada nearly doubled over the course of a decade, from $11.31 in 1998 to $20.77 in 2007.[6] The increase in costs may have at least partly been due to the introduction of more costly antidiabetes drugs to the market. For example, the thiazolidinediones (TZDs) — i.e., rosiglitazone and pioglitazone — represented only 9.4% of all prescriptions for antidiabetes drugs in 2008, yet they accounted for 33% of total expenditures.[13] Given the large, growing population of patients with type 2 diabetes mellitus in Canada, suboptimal use of second-line antidiabetes drugs is likely to have a detrimental effect on both health outcomes and cost effective use of drugs. Therefore, there is a need for clear recommendations based on clinical and cost-effectiveness evidence to guide second-line therapy for patients with type 2 diabetes not adequately controlled on metformin monotherapy.

2.1 Diabetes Mellitus

Diabetes mellitus is a chronic disease characterized by the body's inability to produce sufficient insulin and/or properly use insulin.[14] Type 1 diabetes mellitus occurs in approximately 10% of patients with diabetes, and it results when little or no insulin is produced by the body.[15] Type 2 diabetes mellitus is a metabolic disorder caused by varying degrees of insulin resistance; the body usually produces insulin, but is unable to use it properly.[14] When inadequately managed, diabetes is likely to result in poor glycemic control.[14] Impaired glycemic control, if prolonged, may result in

diabetes-related complications (e.g., ischemic heart disease, stroke, blindness, end-stage renal disease, lower limb amputation).[16,17]

The global prevalence of diabetes is estimated to be 246 million and is projected to increase to 380 million by 2025.[18] In 2005/2006, approximately 1.9 million (5.9%) Canadians aged 20 years and older had diagnosed diabetes.[19] However, it is estimated that 2.8% of the general adult population has undiagnosed type 2 diabetes mellitus,[1] and the true prevalence of diabetes may approach 2.0 million.[20]

2.1.1 Technology description — second-line antidiabetes drugs

Seven classes of antidiabetes drugs that may be used as second-line therapy for patients with type 2 diabetes inadequately controlled on metformin monotherapy are available in Canada: sulfonylureas, meglitinides, a-glucosidase inhibitors, TZDs, incretin agents, weight-loss agents, and insulins (human and insulin analogues). Agents belonging to an eighth class, amylin analogues, are currently not available in Canada. These second-line antidiabetes drugs are presented in Table 1.

Table 1: Classes of Second-Line Antidiabetes Drugs

Drug Class	Products	Mechanism of Action and Clinical Use
Sulfonylureas	Gliclazide (Diamicron, Diamicron MR, Gen-Gliclazide, PMS-Gliclazide); glimepiride (Amaryl); glyburide/glibenclamide (DiaBeta, Euglucon, Gen-Glybe, Novo-Glyburide, Nu-Glyburide, PMS-Glyburide, ratio-Glyburide, Sandoz Glyburide); chlorpropamide (Apo-Chlorpropamide); tolbutamide (Apo-Tolbutamide); Glipizide (Glucotrol, Glucotrol XL, GlipiZIDE XL)[21,22] (not marketed in Canada)	• Sulfonylureas stimulate insulin secretion from the beta cells of the pancreas. • Indicated for use alone or in combination with other oral agents or insulin in the management of type 2 diabetes mellitus.
Meglitinides	Repaglinide (GlucoNorm); nateglinide (Starlix)	• Similar mechanism of action as sulfonylureas; i.e., stimulation of pancreatic insulin release. • Administered at each meal to decrease postprandial plasma glucose. • Indicated as monotherapy or in combination with metformin or rosiglitazone for patients with type 2 diabetes mellitus when hyperglycemia cannot be controlled satisfactorily by diet and exercise alone.
Alpha-glucosidase inhibitors	Acarbose (Glucobay); miglitol (Glyset)[21,23,24] (not marketed in Canada)	• Decrease postprandial plasma glucose levels by inhibiting alpha-glucosidase activity. • Indicated as monotherapy for the management of blood glucose levels in patients with type 2 diabetes mellitus that is inadequately controlled by diet alone. Both agents may also be used in

Table 1: Classes of Second-Line Antidiabetes Drugs		
Drug Class	**Products**	**Mechanism of Action and Clinical Use**
		combination with sulfonylurea, metformin, or insulin to improve glycemic control in patients with type 2 diabetes mellitus.
Thiazolidinediones	Rosiglitazone (Avandia); pioglitazone (Actos)	• Agonists of peroxisome proliferator-activated receptor-gamma (PPARγ). • Decrease insulin resistance in the periphery and liver, thereby increasing insulin-dependent glucose uptake and decreasing hepatic glucose output. • Indicated as monotherapy or in combination with a sulfonylurea or metformin in patients with type 2 diabetes mellitus not controlled by diet and exercise alone. • Use of rosiglitazone in combination with metformin and a sulfonylurea (i.e., triple therapy) or insulin is not indicated for safety reasons.
Incretin agents	DPP-4 inhibitors: sitagliptin (Januvia); saxagliptin (Onglyza), a GLP-1 analogue; vildagliptin (Galvus) (not marketed in Canada) DPP-4 inhibitors: sitagliptin (Januvia); saxagliptin (Onglyza) (a GLP-1 analogue); vildagliptin (Galvus) (not marketed in Canada)[25]	• Sitagliptin is a potent and highly selective inhibitor of DPP-4, an enzyme that metabolizes incretin hormones including glucagon-like peptide-1 and glucose-dependent insulinotropic peptide. DPP-4 inhibitors increase insulin release and decrease glucagon levels by enhancing the effect of incretins. • Sitagliptin is indicated in combination with metformin in adult patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy. • Vildagliptin has a similar mechanism of action to sitagliptin. • Exenatide is a glucagon-like peptide-1 analogue that is administered by subcutaneous injection.[25-28]
Weight-loss agents	Orlistat (Xenical); sibutramine (Meridia)	• Both orlistat and sibutramine are indicated for patients with type 2 diabetes mellitus with a body mass index ≥ 27 kg/m^2. • Orlistat is a reversible inhibitor of gastric and pancreatic lipases that inhibits fat absorption from the gastrointestinal tract. • Sibutramine is a serotonin-norepinephrine reuptake inhibitor that has been shown to reduce body weight through two actions: reduction of food intake through enhancement of satiety and increased energy expenditure by induction of thermogenesis. • Weight loss induced by orlistat and sibutramine improves glucose intolerance and glycemic control in patients with diabetes.

Table 1: Classes of Second-Line Antidiabetes Drugs		
Drug Class	**Products**	**Mechanism of Action and Clinical Use**
		• Orlistat can be used in combination with antidiabetes drugs to improve blood glucose control in overweight or obese patients with type 2 diabetes mellitus that is inadequately controlled by diet, exercise, and one or more of a sulfonylurea, metformin, or insulin.
Human insulins	Short-acting (Humulin R, Novolin ge Toronto) Intermediate-acting: neutral protamine Hagedorn insulin (NPH) (Humulin-N, Humulin 30/70, Novolin ge NPH, Novolin ge 30/70, Novolin ge 40/60, Novolin ge 50/50); lente insulin (no longer available in Canada) Long-acting: ultralente insulin (no longer available in Canada)	• Human insulins have the same amino acid sequence as endogenously secreted insulin and are prepared using recombinant DNA technology.
Insulin analogues	Rapid-acting insulin analogues: insulin lispro (Humalog, Humalog Mix); insulin aspart (NovoRapid, NovoMix 30); insulin glulisine (Apidra) Long-acting insulin analogues: insulin glargine (Lantus); insulin detemir (Levemir)	• Alterations in the amino acid sequence of human insulin were introduced to develop agents that more closely mimic the time-action profile of endogenously secreted basal and postprandial insulin. • Rapid-acting insulin analogues mimic the short duration of action of endogenous postprandial insulin in non-diabetic patients. • Long-acting insulin analogues provide a prolonged, non-fluctuating basal level of insulin activity.
Amylin analogues	Pramlintide (Symlin) (not marketed in Canada)	• Pramlintide is an injectable analogue of amylin, a small peptide hormone released postprandially into the bloodstream by the ß-cells of the pancreas, along with insulin.[2,29] Like insulin, amylin is deficient in individuals with diabetes. • By augmenting endogenous amylin, pramlintide aids in the absorption of glucose by slowing gastric emptying, promoting satiety, and inhibiting inappropriate secretion of glucagon.

2.1.2 Current practice and knowledge regarding second-line antidiabetes drugs for patients with diabetes inadequately controlled on metformin

An understanding of the practices, beliefs, and perceptions of health care practitioners and patients with type 2 diabetes is required in order to identify gaps between evidence-based optimal use of second-line antidiabetes drugs and real-world practice, and to target such gaps effectively. A number of studies have assessed general attitudes of providers and patients with type 2 diabetes regarding antidiabetes therapy, particularly with respect to the challenges of initiating insulin.[30-41] However, perceptions related to second-line agents and the considerations involved in selecting second-line agents have not, to our knowledge, been reported previously. In this study, we undertook a qualitative study to explore this area through focus groups and phone interviews with family physicians, diabetes specialists, pharmacists, diabetes educators, nurse practitioners, and patients with type 2 diabetes in Canada.

3 OBJECTIVES

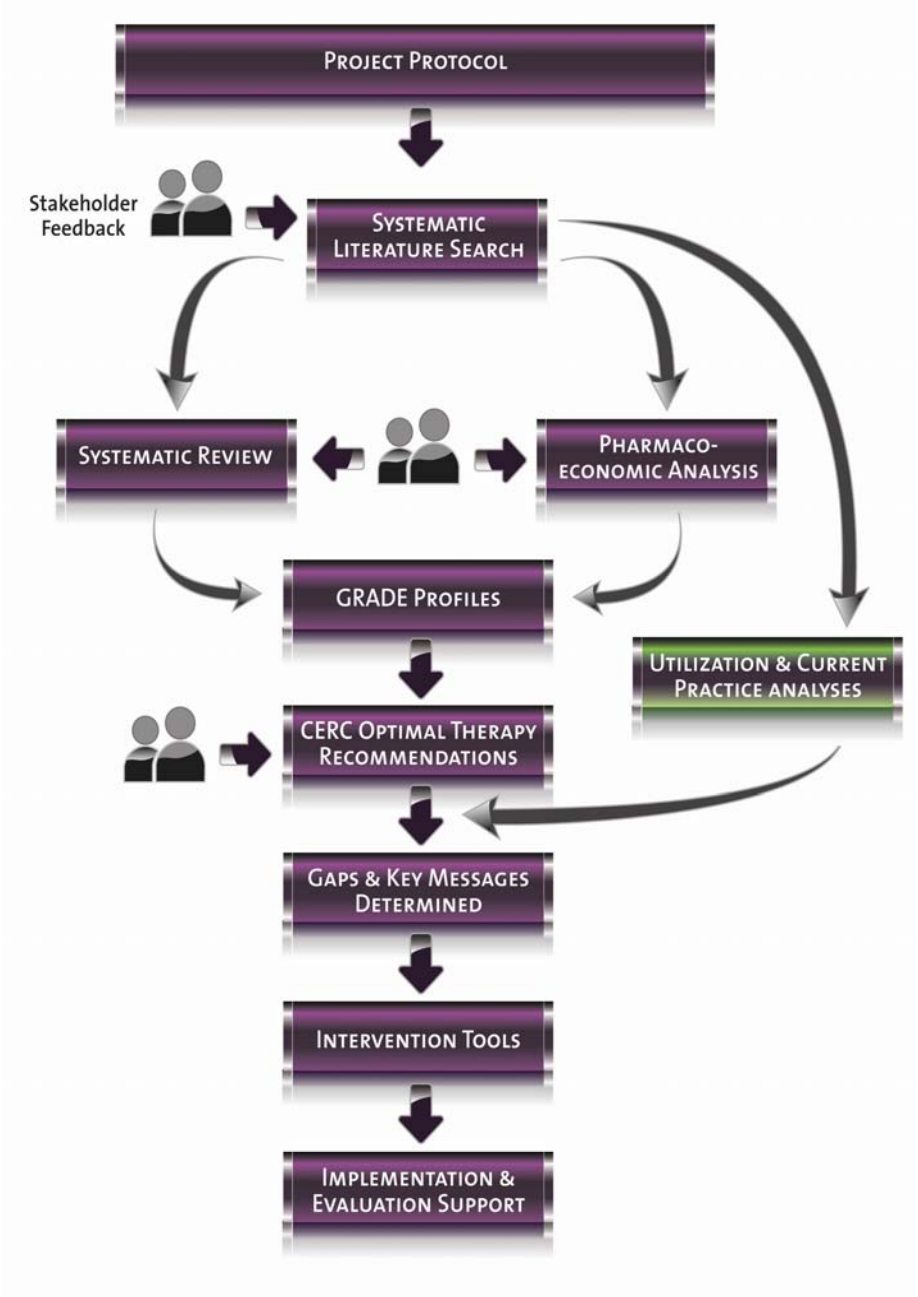
To explore the current views, beliefs, experiences, and practices of patients and health care professionals (i.e., diabetes educators, pharmacists, nurse practitioners diabetes specialists, and family physicians) relative to initiation and selection of second-line therapies for patients with diabetes inadequately controlled on metformin.

4 PROJECT OVERVIEW

Once a topic is selected, CADTH undertakes activities related to key areas in the procedure. The CAC provides advice and guidance throughout the process, from topic identification through to supporting intervention and evaluation tools. CERC, as described in Section 1.0, provides expert advice and recommendations on the topic area relating to the identification, evaluation, and promotion of optimal prescribing and use of drugs. A broad range of stakeholders are invited to provide feedback at key stages in the CADTH process.

To identify and promote the implementation of evidence-based and cost-effective optimal therapy in the prescribing of second-line therapies, CADTH follows the process outlined in the flow chart to the right.

This report represents the Current Practice Analysis step (green box in flow chart) toward the identification of practice and knowledge gaps related to the prescribing of second-line therapy for patients with type 2 diabetes inadequately controlled on metformin.



5 RESEARCH QUESTIONS

The questions asked of participants in the study broadly considered three closely related areas:

1) What are the main considerations of prescribers, influencers, and patients with type 2 diabetes in determining whether a second-line agent should be added to metformin monotherapy?
2) What are the main considerations of prescribers, influencers, and patients with type 2 diabetes in selecting a second-line agent?
3) How are the various second-line agents perceived by prescribers, influencers, and patients with type 2 diabetes?
4) What are the perceived barriers to accessing appropriate second-line agents?
5) What are the main sources of information that health care providers and patients turn to for information on second-line agents? Which of these are preferred for obtaining information?

6 METHODS

CADTH retained Vision Research Inc. to undertake a series of focus groups and interviews with health care professionals (i.e., family physicians, diabetes specialists and nurse practitioners, pharmacists, and diabetes educators) and patients with type 2 diabetes who are currently undergoing drug therapy (i.e., those who have started on metformin monotherapy and have since added a second-line agent).

Potential participants from the health care provider audiences were randomly selected using commercially available lists and screened via telephone to determine their profile and interest in participating. Potential participants from the diabetes patient audience were randomly selected from households listed in the telephone directory. Potential participants were contacted via telephone to explain the study and secure informed consent to participate. Screening questions were used to ensure the profile of participants fit the requirements of the study (see Appendix A for the recruitment screeners).

To assist with recruitment and to recognize the time commitment required for the groups, financial compensation was offered to all participants in the focus groups and interviews. The amounts varied according to industry standards of what is required to effectively motivate potential participants to be part of the study, and to recognize the greater commitment involved in travelling to a focus group facility and undertaking a 90-minute group, as compared with undertaking a 40-minute interview over the phone. A higher amount of compensation was offered to rural focus group participants to recognize the greater travelling time and distance involved.

No Research Ethics Board approval was secured for this study. The study adhered to principles of the Tri-Council Policy Statement (TCPS): *Ethical Conduct for Research Involving Humans*.[42] Participation was strictly voluntary and based on written informed consent freely given by all research participants. The privacy and confidentiality of all participants was protected at every stage of the research.

A total of eight in-person focus groups were conducted with family physicians, pharmacists, diabetes educators, and patients from Ottawa, Ontario and Halifax, Nova Scotia. In addition, phone interviews were conducted with diabetes specialists and nurse practitioners in Ontario and Atlantic Canada. In this case, one-on-one interviews and a wide geographic reach was the preferred approach, as a smaller number of such practitioners overall made it unlikely that sufficient numbers could be recruited for local focus groups. All sessions were audio-recorded and transcribed with prior consent. The groups and interviews were guided by a pre-determined and

approved list of questions that were, at times, common for all participants, and at other times, specialized by audience type (please see Appendix B for the moderator's guides).

A thematic analytic approach was used to analyze the results. Themes were identified based on prevalence among the responses of all participants and organized around the structure of the moderator's guides. In analyzing the data, the focus was not only on prevalence, but also on range, indicating where participants diverged and noting the variety of responses. The overall results are presented first, followed by discussion of the results for each participant type.

7 RESULTS

A total of 74 individuals participated in this study. Study participation by group, location, and type of interaction (i.e., focus group versus phone interview) is shown in Table 2.

Table 2: Study Participation by Group, Location, and Type of Interaction

City	Family Physicians	Pharmacists	Diabetes Educators	Patients	Diabetes Specialists	Nurse Practitioners	Total
	Focus Groups				Phone Interviews		
Ottawa/ Ontario	7 4 men, 3 women	7 3 men, 4 women	7 7 women	7 4 men, 3 women	6 4 men, 2 women	4 4 women	**38**
Halifax/ Atlantic Canada	8 7 men, 1 woman	7 3 men, 4 women	8 8 women	7 3 men, 4 women	2 1 man, 1 woman	4 4 women	**36**
TOTAL	**15**	**14**	**15**	**14**	**8**	**8**	**74**

Sample quotations illustrative of central themes are presented in Appendix C for health care providers, and Appendix D for patients with diabetes.

7.1 Findings for Prescribers

7.1.1 Initial decision to add a second-line agent

Physicians, diabetes specialists, and nurse practitioners were unanimous in pointing to metformin monotherapy as the first-line therapy of choice for the vast majority of patients. The only exceptions were where metformin is contraindicated for a particular patient (i.e., kidney disease, heart failure) or when A1C levels are so high that the prescriber opts to begin with two agents or insulin rather than monotherapy. Prescribers pointed to the low cost, the well-known and modest side effects, the weight-loss benefits, and the overall effectiveness of metformin as the reasons behind the selection. Prescribers also suggested that monotherapy, while perhaps not ideal for patients with more severe symptoms, has the advantage of allowing the prescriber to pinpoint the cause of side effects more easily as other oral agents are added to the patient's therapy.

Prescribers look primarily to glucose levels (in particular A1C) when determining if the time has arrived to add or switch to a second-line agent. An inability to achieve glycemic targets once the maximally effective dosage (ranging from 2 grams to 2.5 grams) of metformin has been reached is what prompts most prescribers who participated in this study to move to second-line therapy. The length of time since the patient began metformin monotherapy is also an important factor that many of the prescribers discussed. We note considerable variation among prescribers regarding

the amount of time (ranging from "a couple of weeks" to six months) they will keep with metformin monotherapy before moving on to a second-line agent. Prescribers also reported that they considered the side effects from metformin experienced by patients (especially gastrointestinal), and the existence of comorbid conditions (i.e., heart disease, hypertension), in determining whether a second-line agent was indicated. Finally, some prescribers indicated they consider the patient's ability to pay for second-line therapy (i.e., access to public or private insurance), as well as their cognitive ability to manage more complex therapy, when deciding to make the move to second-line therapy.

Prescribers were unanimous in their preference for adding a second-line agent to metformin rather than switching from metformin entirely. This approach allows for a cumulative effect (since agents have different mechanisms of action) and allows the prescriber to isolate the cause of adverse side effects. Prescribers suggested they would only switch to a second-line agent if there were serious adverse effects associated with metformin.

7.1.2 Selection of second-line agents

Prescribers described a complex and integrated decision-making process they undertake when selecting a second-line agent. Most consider overall efficacy in achieving glycemic control first and foremost. In addition, prescribers consider the longer-term health risks of second-line agents. Many expressed concerns, for example, regarding the impact of sulfonylureas on the pancreas. Others considered the risks of heart disease and reduced bone density associated with thiazolidinediones (TZDs), although the concern was not universal, as some alluded to research calling these risks into question. Prescribers also take into account the risk of acute side effects such as hypoglycemia (in patients taking sulfonylureas or insulin) and weight gain (in patients taking sulfonylureas, TZDs, or insulin) as they make their choice of second-line agents. Many prescribers, depending on the province in which they practice, also considered a patient's ability to afford a second-line agent (i.e., is it covered by their public or private insurance plan) when making their selection. Newer classes of second-line agents, such as TZDs and dipeptidyl peptidase-4 (DPP-4) inhibitors, were singled out as more expensive and less likely to be covered or included on provincial formularies. Finally, some prescribers pointed to convenience and patient preference as being factors they consider when selecting a second-line agent; once-daily insulin, meglitinides, or products that combine multiple second-line agents in a single dosage form were singled out for this advantage. On the other hand, some prescribers suggested that patients expressed concerns about agents that have received negative coverage in the news media due to safety issues (i.e., TZDs). Table 3 summarizes the *perceived* advantages and disadvantages of each class of second-line agents that were most often expressed by the prescribers who participated in this study.

Table 3: Advantages and Disadvantages of Second-Line Antidiabetes Agents Commonly Expressed by Prescribers, By Drug Class		
Class	**Perceived Advantages**	**Perceived Disadvantages**
Sulfonylureas	▪ Efficacious (% drop in A1C) ▪ Work faster to lower A1C ▪ Well-known side effect profile ▪ Low cost	▪ Weight gain ▪ Effects not as durable as other agents ▪ Risk of hypoglycemia — May be especially problematic for geriatric patients ▪ Risk of pancreatic overstimulation that may speed the decline of insulin secretory ability
Thiazolidinediones	▪ Efficacy ▪ No risk of hypoglycemia ▪ Lack of pancreatic overstimulation ▪ Works well with other drugs ▪ Works well in combination with sulfonylureas	▪ Slower reduction in hemoglobin A1C ▪ Risk of heart failure ▪ Patient fear, preference, and adherence due to negative media coverage ▪ Lack of government coverage ▪ Weight gain ▪ Fluid retention ▪ Risk of fracture ▪ Contraindicated for patients with edema ▪ High cost
Incretin Agents	▪ Less risk of hypoglycemia ▪ Less risk of pancreatic overstimulation; preserves pancreatic function ▪ Complements metformin and TZDs well ▪ Helps patients maintain or lose weight by helping them feel full sooner ▪ Popular with patients based on what they hear from friends, family, and media ▪ Good at controlling post-meal blood glucose	▪ Limited effect on A1Cs ▪ Relatively new — lack of data on long-term risks ▪ High cost ▪ Not covered by provincial formularies ▪ Gastrointestinal side effects
Meglitinides	▪ Convenience and patient adherence ▪ Acts quickly so can be taken with meals	▪ Not as efficacious as other agents ▪ Not covered by provincial formularies
α-glucosidase inhibitors	▪ Good in early diabetes ▪ Weight neutral or may cause some weight loss	▪ Less than 1% drop in A1C ▪ Gastrointestinal side effects
Insulins	▪ Efficacious (more than 2% drop in A1C) — recommended when A1Cs are very high (i.e., above 9 or 10%) ▪ No “highest dosage” ▪ Once-a-day dosing of basal insulins improves patient adherence	▪ Patient fear (especially of needles) and sense of failure — insulin as “the last resort” ▪ Weight gain ▪ Some prescribers feel the need for a specialist consult to initiate insulin

Table 3: Advantages and Disadvantages of Second-Line Antidiabetes Agents Commonly Expressed by Prescribers, By Drug Class		
Class	**Perceived Advantages**	**Perceived Disadvantages**
	▪ A "natural" way to control blood glucose ▪ Many insulins covered by insurance plans ▪ Effective when oral agents are not	▪ Newer insulins not covered ▪ Multiple doses of insulin require a "sophisticated" patient ▪ Requires self-monitoring of blood glucose ▪ Risk of hypoglycemia

A1C = glycosylated hemoglobin; TZD = thiazolidinediones

7.1.3 Insulin as a second-line agent

Insulin is rarely used as a second-line agent by the prescribers who participated in this study. Prescribers generally opt to switch to insulin only when the patient's A1C level remains high (i.e., at or in excess of 7% to 9%) and when other drug classes have proven ineffective. Prescribers tended to report a preference for nighttime basal insulin, pointing to its convenience and their perception that patients will be more likely to adhere to the prescribed therapy.

7.1.4 Barriers to access

Regarding patient barriers to second-line therapies, prescribers generally agreed that the main barrier they perceived was the cost of treatment and the extent of coverage by drug plans. Prescribers also pointed to the challenge of managing complex regimens that can include multiple oral agents (e.g., treatment of diabetes and co-morbid conditions), multiple injections, and regular monitoring (i.e., self-monitoring of blood glucose [SMBG]) by the patient. The complexity can be beyond the cognitive abilities, dexterity, and available time for many patients. Finally, a number of prescribers pointed to the lack of information and education on certain agents as a possible barrier that would discourage prescribers from recommending these to their patients.

7.1.5 Sources of information on second-line therapy

Prescribers pointed to a number of different sources that they trust and to which they turn for information on second-line therapy. Continuing medical education sessions (CMEs), professional journals, and professional websites were all singled out as quality sources. Family physicians pointed in particular to CME sessions featuring reputable diabetes specialists as particularly influential. Prescribers also indicated that the information distributed by pharmaceutical companies was another primary source of up-to-date information on specific drugs, though some indicated they exercise caution when assessing the information, given the vested interests involved.

Prescribers differed somewhat in their preferred methods of receiving information. While family physicians preferred CMEs and medical letters, specialists expressed a preference for CMEs, and nurse practitioners were almost unanimous in saying that they preferred to receive information electronically, either by email or via websites.

By far, the most significant gap in knowledge identified by prescribers relates to the possible long-term adverse effects of the newer oral agents. Many cited research linking TZDs to an increased risk of heart failure and bone density loss as cause for concern and as the reason for a more cautious approach to newer oral agents, including DPP-4 inhibitors.

7.2 Findings From Influencers (Health Care Practitioners)

7.2.1 Choosing a second-line agent

Cost and the list of drugs covered by government formularies and insurance plans were mentioned as significant limiting factors in the choice of second-line therapy by nearly all pharmacists and diabetes educators who participated in this study.

Also high on the list of factors to consider were the short-term side effects and risks of particular agents, with emphasis on the risk of hypoglycemia, especially in the case of elderly patients. Weight gain was also cited as an important side effect to consider. As was the case with prescribers, the risks of longer-term adverse effects were considered by influencers (in particular, diabetes educators). Here again, the participants' experiences with rosiglitazone has contributed to a sense of unease with using new medications whose long-term side effects have not yet been clearly proven.

Influencers reported that they also consider the likelihood of patient adherence when recommending a second-line agent. Participants called attention to convenience and the ease of use as important contributors to adherence, as well as patient education. Patients who understand their condition and its health risks are more likely to adhere to their prescribed course of action.

Many of the influencers who participated in the study echoed the sentiments of prescribers, calling for an integrated approach to prescribing that considers all of these factors and arrives at an individualized approach for each patient.

7.2.2 Insulin as a second-line agent

Most influencers agreed that adding insulin as a second-line therapy has many advantages and is increasingly being employed as a therapeutic strategy. Many diabetes educators questioned the usefulness of oral agents that could, they suggested, cause further harm to the pancreas. Pharmacists spoke of how patients soon discover that administering insulin is not as difficult or as painful as they feared. Several diabetes educators also suggested that insulin empowers patients and encourages them to "take control" of their condition on their own. Much like the prescribers, the majority of influencers agreed that the logical first step in initiating insulin is a single dose of basal insulin at night, pointing to the ease and convenience of this approach.

Influencers also suggested that physicians need to reconsider how they characterize insulin when discussing options with their patients, refraining from positioning it as a "last resort" or using the "threat" of insulin as a negative motivator to help patients follow their prescriptions for diet, lifestyle, and oral agents. Some of the drawbacks to insulin cited by this group of participants include the cost of needles, the need to continually increase the dosage, the risk of hypoglycemia, and the complexity of calculating dosages. It is also worth noting that several influencers suggested they see a trend towards more prescribers turning to insulin as a second-line agent. Table 4 summarizes the *perceived* advantages and disadvantages of different classes of second-line agents that were most often expressed by the pharmacists and diabetes educators who participated in this study.

Table 4: Advantages and Disadvantages of Second-Line Antidiabetes Agents Commonly Expressed by Pharmacists and Diabetes Educators.		
Class	**Perceived Advantages**	**Perceived Disadvantages**
Sulfonylureas	▪ Low cost ▪ Newer versions (i.e., Diamicron MR) are released more slowly and can lessen the risk of hypoglycemia ▪ Once-daily dosage for some agents ▪ Well-known side effect profile ▪ Long-term safety is backed by ample research	▪ Pancreatic overstimulation and possibility of more rapid reduction in insulin secretory ability ▪ Risk of hypoglycemia ▪ Not recommended for elderly patients or those with congestive heart failure
Thiazolidinediones	▪ Efficacy ▪ More user-friendly in terms of timing and other requirements ▪ Reduces required dosage of insulin	▪ Long-term risk of adverse effects such as heart failure ▪ Edema ▪ Expensive
Incretin Agents (especially DPP-4 Inhibitors such as Januvia)	▪ No risk of hypoglycemia ▪ Convenience — once-daily dosage ▪ Less risk of weight gain	▪ Expensive ▪ No data on long-term health risks ▪ Many physicians not yet familiar with and comfortable with this class
Meglitinides	▪ Convenience — take with the meal	▪ Not covered by public drug plans
α-glucosidase inhibitors	▪ None cited	▪ Gastrointestinal side effects
Insulins	▪ Patients feel "in control" as they can adjust dosage and timing ▪ Give the pancreas a break — help to preserve it ▪ No need to take multiple oral agents ▪ No risk of gastrointestinal side effects ▪ No risk of kidney or liver side effects ▪ Maximum effect on lowering A1C levels	▪ Patient fear of needles ▪ Perception that insulin is the "treatment of last resort" ▪ Cost of needles ▪ Need to continually increase dosage ▪ Complexity of calculating dosages ▪ Fear reduces adherence ▪ Doses continually need to be increased due to progressive insulin resistance

7.2.3 Access to optimal therapy

Influencers differed somewhat in their assessment of whether or not patients with type 2 diabetes can access the appropriate second-line therapies. Generally speaking, diabetes educators did not feel that patients with type 2 diabetes are able to access the appropriate second-line therapies they require, citing costs and formulary restrictions as the main barriers. Several educators also felt that the physician's perception of what works might also play a role in whether or not patients have access to the appropriate second-line therapies. The pharmacists who participated in the study were somewhat more positive in their assessment, suggesting that the majority of patients can indeed access appropriate therapies. Pharmacists and diabetes educators agreed that psychological barriers can prevent patients from accessing appropriate second-line therapies. These barriers include the patient's willingness to adhere to a medication, and a physician's

comfort level in prescribing certain medications. Lack of education among patients or their physicians on the range of options available was also identified as a possible barrier.

7.2.4 Sources of information on second-line therapies

Much like prescribers, influencers pointed to a range of different sources of information they turn to and trust. Participants pointed to workshops, Canadian Diabetes Association (CDA) guidelines, and various professional and scientific publications and professional websites as trusted sources. Diabetes educators also pointed to diabetes specialists as influential sources of information. Influencers, like prescribers, acknowledged that pharmaceutical representatives can be an important source of information, especially on newer options, but that the information can be biased.

When asked to identify any gaps in knowledge, influencers reiterated what prescribers told us about newer drugs regarding the lack of data on long-term outcomes.

7.3 Findings for Patients

7.3.1 The move to second-line therapy

Patients described a range of personal experiences with oral agents and insulin to manage their diabetes. Nearly all began with metformin as a first-line therapy, before adding second-line agents over time. Most patients immediately pointed to an inability to bring their blood glucose levels to target as the reason a second-line agent was added, echoing the comments of prescribers on this topic.

Patients reported experiencing a range of sentiments when their care provider indicated it was time to add a second-line agent. Many expressed disappointment and anxiety at the news, perceiving the need to add a second-line agent as a personal "failure." Other patients expressed confidence in their care provider, which translated into confidence in, and acceptance of, the addition of a second-line agent. Many patients expressed concerns about the possible side effects of second-line agents, with particular attention to hypoglycemia and weight gain.

7.3.2 Sources of information

Patients differed widely on the extent to which they felt informed about second-line agents, their risks and benefits. Some clearly wanted to know more. Others lamented not receiving enough time and attention from their family physician to learn about this information and have questions answered.

The Internet emerged as the primary source of impartial information for patients. Not all had full confidence in these online sources; however, websites of well-known institutions tended to generate greater confidence. Many patients also turned to health professionals for information — notably pharmacists and physicians — although this tended to depend on the nature of the relationship the patient had with that health professional (i.e., time and attention they receive) and the extent to which they trusted the profession overall.

7.3.3 Access to optimal therapy

Many of the patients who participated in this study felt they were indeed receiving the medications they needed. None pointed to a specific agent as being optimal, but that was somehow out of reach. Other patients pointed to uncertainty around this question, suggesting that

a lack of knowledge of their options could be a barrier to their receiving the optimal medications. Some patients returned to the sentiments they had expressed earlier about not having the required time and attention of their family physician. In addition, some pointed to financial barriers, with a small number of patients indicating that they had been prescribed a drug that they could not afford to take.

8 DISCUSSION

8.1 Overall Findings

8.1.1 The need for an integrated model of decision-making

Nearly all prescribers and influencers agreed that overall efficacy in reducing blood glucose levels (principally A1C) is paramount in selecting a second-line therapy, although the primacy of this factor did not necessarily lead everyone to the same choices for second-line agents. (For example, diabetes educators were more favourable to insulin as a second-line agent than others.) This factor was closely followed by three additional factors that were each discussed and considered by participants:

- the cost of the medication and the extent to which the patient can afford it, given his or her income and insurance coverage
- the short-term side effects related to the therapy, with particular attention to hypoglycemia, weight gain, and gastrointestinal side effects
- the longer-term adverse effects related to the therapy, in particular the risk of heart disease and fractures, and the long-term impact on the pancreas' ability to secrete insulin.

A final aspect considered by prescribers and influencers is the impact of the therapy on the patient's psychological well-being and lifestyle. Different therapies vary in terms of the level of dexterity required, pain or stress imposed, and time required for administration and monitoring. Participants consider each factor to arrive at an individual plan that maximizes the chances of patient adherence.

While efficacy, cost, and adverse effects were considered to some extent by nearly all prescribers and influencers, a considerable degree of variability was evident in the beliefs, perceptions, and considerations that underlie the choice of second-line antidiabetes agents. A consistently applied prescribing model was lacking. In the pharmacy profession, pharmaceutical care has been advocated as a practice model to improve patient care.[43] It consists of a rational and explicit process to identify therapeutic goals in collaboration with the patient and other health care providers, select and monitor drug therapy, and identify drug-related problems. With respect to the choice of a specific agent, the pharmaceutical care approach requires explicit consideration of the evidence of efficacy and safety, patient values and preferences, and costs.[43] Application of some portions of a practice model, such as pharmaceutical care to the choice of second-line antidiabetes drugs, may result in more consistency in prescribing and, perhaps, improved health outcomes and cost-effectiveness.

Patients focused more of their comments on the short-term side effects of different second-line therapies, describing their experiences with hypoglycemia, weight gain, and gastrointestinal side effects. While some mentioned concerns over long-term adverse effects and efficacy, most were prepared to leave these considerations to their physicians. Finally, some patients did mention the high costs of medication and of other aspects (notably blood glucose test strips) of living with diabetes.

8.1.2 The psychological dimensions of moving to second-line therapy

The comments of participants revealed important psychological dimensions for the patient and the prescriber. Participants described the fear that patients can experience with the move to insulin; for example, driven by a fear of needles and concern about insulin as a solution of "last resort." Similarly, patients described the disappointment and sense of failure that accompanies the announcement that a new line of therapy needs to be added. Finally, patients described — often in very emotional terms — the importance of the time and attention of a care provider. Those who benefit from such a strong relationship with a physician, for example, celebrated the fact. On the other hand, patients without the benefit of having someone listen, answer questions, and take time with them expressed frustration and anxiety over the choice of the medications prescribed to them.

Both prescribers and influencers described the psychological dimension of choosing second-line therapy. We heard of the comfort of prescribing medications whose side effects and long-term health impacts are well-known, as compared with the uncertainty surrounding newer alternatives. We also heard of the habits and "clinical inertia"[44] that such comfort and uncertainty can engender, as prescribers "hang on" a little longer with oral agents to delay the move to insulin. We heard of the preference among some prescribers for referring patients to diabetes specialists or diabetes educators for this step. Finally, and perhaps most emphatically, we heard of the frustration prescribers feel when the optimal second-line therapy is out of reach for a patient, either because of costs or provincial formularies/insurance coverage.

These findings point to the importance of appropriate patient education and support as therapeutic decisions regarding diabetes management are taken. Patients need to appreciate the progressive nature of diabetes, so that the need for additional therapy is not seen as a personal failure. Furthermore, the advantages and disadvantages of the available agents need to be discussed with patients so that they can make informed treatment decisions in collaboration with health care providers. The fears and misperceptions associated with insulin, which may lead to delay in insulin initiation, require particular focus. Once again, elements of the pharmaceutical care model may be useful in clinical practice, since it offers an explicit manner in which patients can actively engage in the therapeutic decision-making process.[43]

8.1.3 The guideline gap

The selection of second-line therapies is complex, both medically and psychologically. In this context, the lack of widely recognized guidelines is problematic. While this study revealed a number of widely held views about second-line agents (see Tables 3 and 4), participants did not point consistently to an authoritative source of evidence-based information or guidelines upon which they base these views. Very few participants pointed to any set of guidelines on this aspect of clinical practice. Participants relied, instead, on an individual blend of CME events, opinion leaders, professional journals, and websites, as well as on information received from pharmaceutical representatives (which many approach cautiously but acknowledge as useful nonetheless). The blend of sources was unique to each participant, leading to a diverse set of views and practices regarding second-line therapies.

These findings suggest the need for evidence-based recommendations and resources that prescribers and influencers can use when selecting second-line therapies and counselling patients. Ideally, local opinion leaders (especially diabetes specialists) would be engaged in educating other care providers about such recommendations.

8.2 Results in Relation to Other Studies

To our knowledge, this study is the first to assess perceptions, practices, and beliefs related to the selection of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin. Some of our results correspond to previous studies that have assessed attitudes of physicians towards drug therapy in type 2 diabetes more generally.

8.2.1 Studies involving care providers

Agarwal et. al.[30] conducted interviews with Ontario general practitioners (GPs) to determine the rationale for decisions related to prescribing of insulin to older patients with type 2 diabetes. Like the authors, we also heard from prescribers about how their attitudes about older patients (i.e., their cognitive abilities, manual dexterity, and ability to cope with hypoglycemia) could discourage them from prescribing insulin. Another common theme between the two studies was that prescribers considered their patients' reluctance to use needles and their sense that the move to insulin signals a failure on their part. And, like the authors, we heard that some family physicians lacked experience with initiating insulin and sought the assistance of specialists or local diabetes clinics.

These findings were echoed in two other studies — one, a survey of primary care physicians in the United States,[33] and the second, a focus group study with GPs, GP educators, and practice nurses in the United Kingdom.[38]

8.2.2 Studies involving patients

Nair et. al.[32] conducted individual interviews with patients with type 2 diabetes in Canada. They found that patients generally felt they had received inadequate information about treatment risks and benefits at the time of initiation, and that an ongoing learning process was required on their part. A major theme they uncovered was "I take what I think works for me." This differs somewhat from the findings of this study, where patients tended to express confidence in the recommendations of their care provider ("They're doing this for your health. They're going to make you well."), especially where subjects enjoyed a positive, collaborative relationship with their physician. However, subjects who did not have such a therapeutic relationship expressed similar concerns about lack of information, as in the Nair study. Like the Nair study, we found that patients were concerned about hypoglycemia, were frustrated by medication costs, and desired individualized and attentive care from their physician.

Hayes et. al.[31] conducted focus groups with patients with type 2 diabetes in the United States and reported that inconvenience and inflexibility, as well as the fear of hypoglycemia, were important concerns for patients. Inconvenience did not emerge as a significant theme in our discussions, but was mentioned by patients in relation to the number of oral agents they need to take and the number of times each day they must remember to take these. Where our participants most echoed the sentiments expressed in the Hayes study was in the concern and fear of hypoglycemia induced by antidiabetes therapies.

Lawton et. al.[35] conducted in-depth interviews with Scottish patients with type 2 diabetes and found evidence of attitudes toward oral agents that often match those of the patients in our study. Like Lawton et al., we found that patients experience anxiety and a sense of failure as the condition progresses and the need to augment therapy arises. Our patients also experienced and discussed negative side effects from some oral agents, although not to the extent that participants in the Lawton study did. And, like participants in the Lawton study, patients in our

study expressed a preference for simpler therapy (i.e., fewer pills, fewer times per day) and expressed confidence in the recommendations of their physicians.

The findings from a study by Tjia et. al.[37] involving interviews with patients with diabetes in the United States pointed, as did our study, to the importance of a positive patient-physician relationship. Whereas patients in our study did not seem to focus as much of their discussion with physicians on adherence, they mirrored the patients in the Tjia study in discussing possible side effects with their physicians. Also, like the patients in the Tjia study, the patients we spoke with expressed frustration with complex regimens and a preference for simpler regimens.

Finally, Lai et. al.[39] conducted in-depth interviews with patients in Taiwan. They reported significant concerns regarding the toxic effects of antidiabetes drugs on the kidneys and strategies for eliminating them. The fact that these concerns were not voiced by participants in our study may reflect cultural differences in how the risks and benefits of medications are perceived.

8.3 Strengths and Limitations

The strength of this study lies in the quality and richness of the comments offered by participants. Whether in focus groups or interviews, the participants were engaged, informed, and willing to share their sentiments, experiences, and opinions with the moderator. The number and depth of discussions with prescribers, with influencers, and with patients allowed us to achieve saturation on all the key points we set out to address. Another strength is the extent to which the principal findings of this study correspond to findings from numerous other studies undertaken inside and outside of Canada.

The limitations to this study stem from the small number of participants and inherent self-selection bias. Participants were invited and remunerated to participate in the study. We also note that participants were drawn from Ontario and Atlantic Canada (with the majority from the latter group being drawn from Nova Scotia). As provincial formularies and public insurance plans can vary from one province to another, the focus on a small number of provinces is a limiting factor. Practice patterns may also vary across regions for other reasons.

The reliance on patient recall is also a possible limiting factor for this study. Some had begun a second-line therapy years before the focus groups were held; therefore, their recollection of the exact regimen that was prescribed and their experiences may have been imperfect.

A number of next steps are suggested by the findings of this study. Additional qualitative research in other jurisdictions could be undertaken to explore the extent to which regulatory and funding differences influence views and practices related to second-line therapy. Quantitative research could be used with more precision and potential for extrapolation to delve into some of the findings from this study. These studies could cover topics such as:

- extent of the prescriber's knowledge about different second-line therapies
- agreement or disagreement with the advantages and disadvantages of different classes of second-line therapies, as expressed by the participants in this study
- relative influence of different, specific sources of information on the topic of second-line therapies
- patient satisfaction with their physician-patient relationship and the effect on their level of knowledge about, and confidence in, their prescribed second-line therapy.

9 CONCLUSION

Given the high degree of variability in the information sources that prescribers and patients use in determining the choice of second-line therapy, and the heterogeneity in perceived benefits and risks of various agents, the dissemination of evidence-based recommendations and information is required to support prescribers, influencers, and patients with type 2 diabetes inadequately controlled on metformin in the selection of optimal second-line antidiabetes therapies.

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APPENDIX A: RECRUITMENT SCREENERS

Screener — Physicians

(NOTE THE CANDIDATE'S SETTING, STRIVE FOR A MINIMUM OF THREE RURAL PARTICIPANTS PER GROUP)

- ❑ Urban
- ❑ Rural

Hello my name is _____ and I am calling from Vision Research on behalf of the Canadian Agency for Drugs and Technologies in Health — an independent, not-for-profit agency funded by Canadian federal, provincial, and territorial governments. The agency is not linked to industry, and provides impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision-makers.

We are inviting physicians to participate in a study that will seek feedback on issues related to drug therapy in type 2 diabetes, as well as self-monitoring of blood glucose. Your participation would involve a 90-minute focus group at a downtown research facility and we would provide you with an incentive of:

- ❑ For urban physicians — $275
- ❑ For rural physicians — $350

… for your time.

Would you be willing to participate in this study?

- ❑ Yes **(CONTINUE)**
- ❑ No **(THANK & TERMINATE)**

(NOTE THE CANDIDATE'S GENDER, STRIVE FOR A BALANCE OF MALE AND FEMALE)

- ❑ Male
- ❑ Female

Before I confirm your participation, I'd like to ask you a few questions about your practice to ensure we have a balanced sample for the study.

Q1: Which of the following best describes your accreditation as a physician?

A) General Practice
B) Family Physician
C) Specialist (please specify: ❑ Endocrinologist
❑ Internist with a specialty in diabetes
D) Other (please specify: _____)

(IF THE PHYSICIAN IS AN ENDOCRINOLIGIST OR AN INTERNIST WITH A SPECIALTY IN DIABETES, SWITCH TO DIABETES SPECIALIST SCREENER AND SKIP TO Q3)

Q2: As a physician, how often do you recommend initiation or changes to drug therapy for adults with type 2 diabetes?

- ❑ Regularly
- ❑ Only sometimes
- ❑ Never

(IF "Never" — THANK AND TERMINATE)

Q3: Which of the following best describes your type of practice?

- ❑ Solo
- ❑ Group or partnership
- ❑ Hospital
- ❑ Other (please specify: _____)

(PLEASE STRIVE FOR A BLEND OF PRACTICES)

Q4: Which best describes your principal source of professional income?

- ❑ Fee-for-service
- ❑ Salary

(PLEASE STRIVE FOR A BLEND)

CONFIRMATION

Thank you for answering our questions. I would like to confirm your participation in the focus group. The session will last about 90 minutes and will take place on **(REFER TO SCHEDULE)**. Your participation will be helpful in shaping the best practices for drug prescribing in the future and you will receive $275 (urban) or $350 (rural) for taking part. Please note that the information we are gathering from you will be kept strictly confidential and will be protected at every stage of the research process.

Can I confirm your participation in the study?

Yes ☐ **(CONTINUE)** No ☐ **(THANK AND TERMINATE)**

The focus group will take place at: _____TBD_____

It is very important that we consider the perspective of physicians in this study and we are only inviting a very small number of physicians to participate, so your involvement is very important to us. If you are unable to take part in the focus group, please call me at (PROVIDE NUMBER). We'll also be confirming your participation the day before the session. Thank you for your time.

Screener — Diabetes Specialists

Hello my name is _____ and I am calling from Vision Research on behalf of the Canadian Agency for Drugs and Technologies in Health — an independent, not-for-profit agency funded by Canadian federal, provincial, and territorial governments. The agency is not linked to industry, and provides impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision-makers.

We are inviting diabetes specialists to participate in a study that will seek feedback on issues related to drug therapy in type 2 diabetes, as well as self-monitoring of blood glucose. Your participation would involve a 40-minute, one-on-one interview over the telephone and we would provide you with a $350 incentive for your time. Would you be willing to participate in this study?

- ❑ Yes **(CONTINUE)**
- ❑ No **(THANK AND TERMINATE)**

(NOTE THE CANDIDATE'S GENDER, STRIVE FOR A BALANCE OF MALE AND FEMALE)

- ❑ Male
- ❑ Female

(NOTE THE CANDIDATE'S SETTING, STRIVE FOR A BLEND OF RURAL AND URBAN PARTICIPANTS)

- ❑ Urban
- ❑ Rural

Before I confirm your participation, I'd like to ask you a few questions about your practice to ensure we have a balanced sample for the study.

Q1: Which of the following best describes your accreditation as a Diabetes specialist?

A) Endocrinologist
B) Internist with a specialty in diabetes
C) Other (please specify: _____)

Q2: As a specialist, how often do you recommend initiation or changes to drug therapy for adults with type 2 diabetes?

- ❑ Regularly
- ❑ Only sometimes
- ❑ Never

(IF "Never" — THANK AND TERMINATE)

Q3: Which of the following best describes your type of practice?

- ❑ Solo
- ❑ Group or partnership
- ❑ Hospital
- ❑ Other (please specify: _____)

(PLEASE STRIVE FOR A BLEND OF PRACTICES)

Q4: Which best describes your principal source of professional income?

- ❑ Fee-for-service
- ❑ Salary

(PLEASE STRIVE FOR A BLEND)

CONFIRMATION

Thank you for answering our questions. I would like to confirm your participation in the focus group. The interview will last about 40 minutes and will take place on **(REFER TO SCHEDULE)**. Your participation will be helpful in shaping the best practices for drug prescribing in the future and you will receive $350 for taking part. Please note that the information we are gathering from you will be kept strictly confidential and will be protected at every stage of the research process.

Can I confirm your participation in the study?

Yes ☐ **(CONTINUE)** No ☐ **(THANK AND TERMINATE)**

The Interview will take place at: _____TBD_____

It is very important that we consider the perspective of diabetes specialists in this study and we are only inviting a very small number to participate, so your involvement is very important to us. If you are unable to complete the interview, please call me at (PROVIDE NUMBER). We'll also be confirming your participation the day before the interview. Thank you for your time.

Screener — Nurse Practitioners

Hello my name is _____ and I am calling from Vision Research on behalf of the Canadian Agency for Drugs and Technologies in Health — an independent, not-for-profit agency funded by Canadian federal, provincial, and territorial governments. The agency is not linked to industry, and provides impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision-makers.

We are inviting nurse practitioners to participate in a study that will seek feedback on issues related to drug therapy in type 2 diabetes, as well as self-monitoring of blood glucose. Your participation would involve a 40-minute, one-on-one interview over the telephone and we would provide you with a $200 incentive for your time. Would you be willing to participate in this study?

- ❑ Yes **(CONTINUE)**
- ❑ No **(THANK AND TERMINATE)**

(NOTE THE CANDIDATE'S GENDER, STRIVE FOR A BALANCE OF MALE AND FEMALE)

- ❑ Male
- ❑ Female

(NOTE THE CANDIDATE'S SETTING, STRIVE FOR A BLEND OF RURAL AND URBAN PARTICIPANTS)

- ❑ Urban
- ❑ Rural

Before I confirm your participation, I'd like to ask you a few questions about your practice to ensure we have a balanced sample for the study.

Q1: In addition to being a Nurse Practitioner, are you certified as a diabetes educator?

- ❑ Yes
- ❑ No

(IF YES, PLACE IN THE DIABETES EDUCATOR GROUP AND SWITCH TO THAT SCREENER)

Q2: As a Nurse Practitioner, how often do you provide direct care for adults with type 2 diabetes?

- ❑ Regularly
- ❑ Only sometimes
- ❑ Never

(IF "Never" — THANK AND TERMINATE)

Q3: Which of the following best describes your type of practice?

- ❑ Solo
- ❑ Group or partnership
- ❑ Hospital
- ❑ Other (please specify: _____)

(PLEASE STRIVE FOR A BLEND OF PRACTICES)

Q4: Which best describes your principal source of professional income?

- ❑ Fee-for-service
- ❑ Salary

(PLEASE STRIVE FOR A BLEND)

CONFIRMATION

Thank you for answering our questions. I would like to confirm your participation in the focus group. The interview will last about 40 minutes and will take place on **(REFER TO SCHEDULE)**. Your participation will be helpful in shaping the best practices for drug prescribing in the future and you will receive $200 for taking part. Please note that the information we are gathering from you will be kept strictly confidential and will be protected at every stage of the research process.

Can I confirm your participation in the study?

Yes ☐ **(CONTINUE)** No ☐ **(THANK AND TERMINATE)**

The Interview will take place at: _____TBD_____

It is very important that we consider the perspective of nurse practitioners in this study and we are only inviting a very small number to participate, so your involvement is very important to us. If you are unable to complete the interview, please call me at (PROVIDE NUMBER). We'll also be confirming your participation the day before the interview. Thank you for your time.

Screener — Pharmacists

(NOTE THE CANDIDATE'S SETTING, STRIVE FOR A MINIMUM OF THREE RURAL PARTICIPANTS PER GROUP)

- ❑ Urban
- ❑ Rural

Hello my name is _____ and I am calling from Vision Research on behalf of the Canadian Agency for Drugs and Technologies in Health — an independent, not-for-profit agency funded by Canadian federal, provincial, and territorial governments. The agency is not linked to industry, and provides impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision-makers.

We are inviting pharmacists to participate in a study that will seek feedback on issues related to drug therapy in type 2 diabetes, as well as self-monitoring of blood glucose. Your participation would involve a 90-minute focus group at a downtown research facility and we would provide you with an incentive of:

- ❑ For urban pharmacists — $225
- ❑ For rural pharmacists — $300

… for your time.

Would you be willing to participate in this study?

- ❑ Yes **(CONTINUE)**
- ❑ No **(THANK AND TERMINATE)**

(NOTE THE CANDIDATE'S GENDER, STRIVE FOR A BALANCE OF MALE AND FEMALE)

- ❑ Male
- ❑ Female

Before I confirm your participation, I'd like to ask you a few questions about your practice to ensure we have a balanced sample for the study.

Q1: In addition to being a pharmacist, are you certified as a diabetes educator?

- ❑ Yes
- ❑ No

(IF YES, PLACE IN THE DIABETES EDUCATOR GROUP AND SWITCH TO THAT SCREENER)

Q2: As a pharmacist, how often do you provide direct care for adults with type 2 diabetes?

- ❑ Regularly
- ❑ Only sometimes
- ❑ Never

(IF "Never" — THANK AND TERMMINATE)

Q3: Which of the following best describes your principal work setting?

- ❑ Community or retail pharmacy
- ❑ Hospital pharmacy
- ❑ Primary Care Team or Family Health Team
- ❑ Other (please specify: _____)

(PLEASE STRIVE FOR A BLEND OF WORK SETTINGS)

CONFIRMATION

Thank you for answering our questions. I would like to invite you to participate in a focus group. The session will last about 90 minutes and will take place on **(REFER TO SCHEDULE)**. Your participation will be helpful in shaping the best practices for drug prescribing in the future and you will receive $225 (urban) or $300 (rural) for taking part. Please note that the information we are gathering from you will be kept strictly confidential and will be protected at every stage of the research process.

Can I confirm your participation in this study?

Yes ☐ **(CONTINUE)** No ☐ **(THANK AND TERMINATE)**

The focus group will take place at: _____TBD_____

It is very important that we consider the perspective of pharmacists in this study and we are only inviting a very small number of pharmacists to participate, so your involvement is very important to us. If you are unable to take part in the focus group, please call me at (PROVIDE NUMBER). We'll also be confirming your participation the day before the session. Thank you for your time.

Screener — Diabetes Educators

(NOTE THE CANDIDATE'S SETTING, STRIVE FOR A MINIMUM OF THREE RURAL PARTICIPANTS PER GROUP)

- ❑ Urban
- ❑ Rural

Hello my name is _____ and I am calling from Vision Research on behalf of the Canadian Agency for Drugs and Technologies in Health — an independent, not-for-profit agency funded by Canadian federal, provincial, and territorial governments. The agency is not linked to industry, and provides impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision-makers.

We are inviting diabetes educators to participate in a study that will seek feedback on issues related to drug therapy in type 2 diabetes, as well as self-monitoring of blood glucose. Your participation would involve a 90-minute focus group at a downtown research facility and we would provide you with an incentive of (check one):

- ❑ For urban diabetes educators — $200
- ❑ For rural diabetes educators — $275

… for your time.

Would you be willing to participate in this study?

- ❑ Yes **(CONTINUE)**
- ❑ No **(THANK AND TERMINATE)**

(NOTE THE CANDIDATE'S GENDER, STRIVE FOR A BALANCE OF MALE AND FEMALE)

- ❑ Male
- ❑ Female

Before I confirm your participation, I'd like to ask you a few questions about your practice to ensure we have a balanced sample for the study.

Q1: As a diabetes educator, how often do you recommend initiation or changes to drug therapy for adults with type 2 diabetes?

- ❑ Regularly
- ❑ Only sometimes
- ❑ Never

(IF "Never" — THANK AND TERMINATE)

Q2: Which of the following best describes your principal work setting?

- ❑ Clinic
- ❑ Hospital
- ❑ Community care setting
- ❑ Other (please specify: _____)

(PLEASE STRIVE FOR A BLEND OF WORK SETTINGS)

CONFIRMATION

Thank you for answering our questions. I would like to invite you to participate in a focus group. The session will last about 90 minutes and will take place on **(REFER TO SCHEDULE).** Your participation will be helpful in shaping the best practices for drug prescribing in the future and you will receive $200 (urban) or $275 (rural) for taking part. Please note that the information we are gathering from you will be kept strictly confidential and will be protected at every stage of the research process.

Can I confirm your participation in this study?

Yes ☐ **(CONTINUE)** No ☐ **(THANK AND TERMINATE)**

The focus group will take place at: _____TBD_____

It is very important that we consider the perspective of diabetes educators in this study and we are only inviting a very small number of them to participate, so your involvement is very important to us. If you are unable to take part in the focus group, please call me at (PROVIDE NUMBER). We'll also be confirming your participation the day before the session. Thank you.

APPENDIX B: MODERATOR'S GUIDES

Moderator's Guide — Prescribers

NOTE: This moderator's guide was used for focus groups and/or interviews with diabetes specialists, family physicians, and nurse practitioners.

1.0 Introduction

1.1 Before we start, I would like to explain a few things about this study and today's focus group.

- The group will last 60 to 90 minutes.
- There will be observers from CADTH behind the mirror, who are observing so that they can see and hear your comments first-hand and learn as much as possible from the study.
- The group will be audio-recorded to allow for a more detailed report; audio files will remain the property of the research firm and will be erased after 12 months.
- Participation in the group is strictly voluntary and participants need not answer any question that makes them feel uncomfortable.
- The identity of participants will be kept confidential in all aspects of the study and in the final report.
- The study is being undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH) — a not-for-profit agency funded by the federal and provincial governments and mandated by them to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies.
- This study is focusing on the diabetes management topic area.

1.2 Are there any questions or concerns related to this study?

2.0 Second-Line Therapy

I'd like to start by asking you some questions about your opinions and current practice regarding second-line therapy after a patient's metformin therapy has failed.

2.1 For approximately what percentage of patients with type 2 diabetes do you prescribe metformin monotherapy as initial antihyperglycemic therapy? What prompts you to opt for this treatment?

2.2 What criteria do you use to determine whether or not treatment with metformin monotherapy is successful? What constitutes failure of metformin monotherapy?

Probe for: Do you always use the A1C as a surrogate for evaluating treatment efficacy? Probe for: If so, why? If not, what other markers do you use (i.e., fasting blood glucose, post-prandial blood glucose) and why do you prefer these?

2.3 What is the maximal dose and duration of metformin you will normally try before deciding to add or switch to a second agent?

2.4 Is a second agent added to metformin, or is metformin discontinued once the second agent is started? Why do you prefer this approach?

Probe for: Under what circumstances would you discontinue metformin and switch to a different agent rather than adding a second-line agent to the metformin?

2.5 What class of second-line agents do you normally use when adding to, or switching from, metformin?

2.6 Are there particular circumstances under which you would opt for a newer oral antihyperglycemic class (i.e., TZDs or DPP-4 inhibitors) instead of using an agent from an older class (e.g., sulfonylureas) as second-line therapy?

2.7 What are your thoughts on the relative merits of the oral agents? Are there particular oral agents you feel are better than others in terms of:
Overall **efficacy**?
The risk of **weight gain**?
The risk of **hypoglycemia**?
The **cost of therapy** and the patient's drug coverage?
The **patient's preference**?

2.8 Under what circumstances do you opt to add or switch to insulin as a second-line therapy instead of an oral agent?

Probe for: preferences regarding prandial (bolus), basal, basal-bolus combinations, or premixed insulins as second-line therapy.

2.9 Generally speaking, do you feel your patients are able to access appropriate second-line therapies when these therapies are required? If not, what do you perceive as barriers?

Probe for: Formulary restrictions, cost, adherence issues, self-management/burden of care/caregiver issues?

2.10 What would you say are the primary sources of information you use to guide your choice of second-line therapies in type 2 diabetes?

Probe for: Information from pharmaceutical companies.
Probe for: CDA Guidelines.

2.11 What are your thoughts regarding the available evidence to guide the choice of second-line agents? Are there any issues, uncertainties, or controversies you would like to have more information on? If yes, please explain.

2.12 What is your preferred method of receiving information on second-line treatments?

Probe for: Written materials, workshops, lectures, journal articles.

Moderator's Guide — Influencers

NOTE: This moderator's guide was used for focus groups and/or interviews with pharmacists and diabetes educators.

1.0 Introduction

1.1 Before we start, I would like to explain a few things about this study and today's focus group.

- The group will last 60 to 90 minutes.
- There will be observers from CADTH behind the mirror, who are observing so that they can see and hear your comments first-hand and learn as much as possible from the study.
- The group will be audio-recorded to allow for a more detailed report; audio files will remain the property of the research firm and will be erased after 12 months.
- Participation in the group is strictly voluntary and participants need not answer any question that makes them feel uncomfortable.
- The identity of participants will be kept confidential in all aspects of the study and in the final report.
- The study is being undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH) — a not-for-profit agency funded by the federal and provincial governments and mandated by them to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies.

  This study is focusing on the diabetes management topic area.

1.2 Are there any questions or concerns related to this study?

2.0 Second-Line Therapy

I'd like to start by asking you some questions about your opinions regarding second-line therapy after a patient's metformin therapy has failed.

2.1 What are your thoughts on the relative merits of the oral agents used to treat patients with type 2 diabetes? Are there particular oral agents you feel are better than others in terms of efficacy, convenience, or side-effect profile?

2.2 In your opinion, are there any advantages or disadvantages to using newer oral antihyperglycemic agents like a TZD or DPP-4 inhibitors as compared to using an older agent like a sulfonylurea as a second-line therapy once metformin has failed?

2.3 For Diabetes Educators Only:

What are your thoughts on using insulin in patients with type two diabetes, who have failed metformin? Under what situations (if any) should insulin be chosen rather than an oral agent as second-line therapy?

Probe for: preferences regarding prandial (bolus), basal, basal-bolus combinations, or premixed insulins as second-line therapy.

2.4 In your opinion, what are the most important factors that should be considered when a prescriber is choosing a second-line therapy?

Probe for: How important is the risk of weight gain?
Probe for: How important is the risk of hypoglycemia?
Probe for: How important is the cost of therapy and the patient's drug coverage?
Probe for: How important is patient preference?

2.5 Generally speaking, do you feel patients with diabetes are able to access the appropriate second-line therapies they require? If not, what do you perceive as barriers?

Probe for: Formulary restrictions, cost.

2.6 What are the primary sources of information you use to obtain guidance on the choice of second-line therapies in type 2 diabetes?

Probe for: Information from pharmaceutical companies.
Probe for: CDA Guidelines.

2.7 What are your thoughts regarding the available evidence to guide the choice of second-line agents? Are there any issues, uncertainties, or controversies you would like to see more information on? If yes, please explain.

2.8 What is your preferred method of receiving information on second-line treatments?

Probe for: Written materials, workshops, lectures, journal articles.

Moderator's Guide — Patients

NOTE: This moderator's guide was used for focus groups involving patients with type 2 diabetes.

1.0 Introduction

1.1 Before we start, I would like to explain a few things about this study and today's focus group.

- The group will last 60 to 90 minutes.
- There will be observers from CADTH behind the mirror, who are observing so that they can see and hear your comments first-hand and learn as much as possible from the study.
- The group will be audio-recorded to allow for a more detailed report; audio files will remain the property of the research firm and will be erased after 12 months.
- Participation in the group is strictly voluntary and participants need not answer any question that makes them feel uncomfortable.
- The identity of participants will be kept confidential in all aspects of the study and in the final report.
- The study is being undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH) — a not-for-profit agency funded by the federal and provincial governments and mandated by them to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies.

  This study is focusing on the diabetes management topic area.

1.2 Are there any questions or concerns related to this study?

2.0 Second-Line Therapy

I'd like to start by asking you some questions about your opinions regarding medications to control your blood glucose levels.

2.1 What medications do you currently use to control your blood glucose levels? How long were you on metformin and what prompted your doctor to suggest either an addition of other agents or a switch in therapy?

2.2 How did you feel when your doctor told you that you were going to need another medication to control your blood glucose levels?

2.3 Did you have any concerns when your doctor prescribed medication to lower your blood glucose?

Probe for: Were you concerned that some medications might be better or worse than others?
Probe for: Were you concerned about whether or not some drugs might make you gain more weight?
Probe for: Were you concerned that some drugs might make it more likely that you experience hypoglycemia?

2.4 Do you feel your doctor took these concerns into account when prescribing blood glucose-lowering medications?

Probe for: Did you request that a particular medication be prescribed for you? If so, why?
Probe for: Did your doctor fulfill your request? Why or why not?

2.5 Have you looked for information on blood glucose-lowering medications in the past? If so, where did you find good information? What are the best sources out there?

Probe for: Specific websites, organizations, friends and family, advertising.

2.6 Do you feel you have enough information on medications to lower your blood glucose levels? If not, how would you like to receive more information and from whom?

2.7 Do you feel you are receiving the blood glucose-lowering medications you need? If not, what might be preventing you from receiving the medications you need?

APPENDIX C: SAMPLE QUOTES FROM HEALTH CARE PROVIDERS

The following quotes from health care providers help to showcase the central themes observed in the selection of second-line antidiabetes drugs.

Effectiveness

- *"I look at the patent's A1C and their glucose readings. So if their A1C does not come down under 7 after three months of therapy, then it's not successful. I look at their glucose readings and I look at a much shorter time frame than that. If I'm starting somebody on therapy and after several weeks it's clear that their readings are nowhere near target, the 4 to 7 target, then it's not successful. And then I would move to move on in therapy." — Diabetes specialist, Nova Scotia*

- *"I generally add glyburide, Diamicron or rosiglitazone, Avandia. So the sulfonylureas, either Diamicron or the glyburide, will bring down the blood sugars fairly quickly. And it has a different mechanism of action than the metformin. So that would be my main reason for using those, plus they're cheap and/or covered. The Avandia tends to be helpful in people that have insulin resistance and who are obese, and seems to last a long time in terms of preventing the need for other medications down the road. — Diabetes specialist, Ontario*

- *"Certainly we're looking at the blood sugar control, so that's the hemoglobin A1C. Certainly direct me there. You also have to listen to the patient. Sometimes there can be side effects with this drug. So if they have any of the severe GI effects from the metformin, then that would warrant moving more quickly to another agent and not going to the maximum with metformin." — Nurse Practitioner, Ottawa*

- *"I would think, above all else, probably efficacy. A factor I would consider in the context of that client. So it's sort of customizing the therapy to that particular client." — Nurse Practitioner, Ottawa*

- *"If they've had diabetes for a long time, I tend to find some classes don't work as well. Like the Januvia, for instance, all my longer-term diabetics, whenever I try them on that one, it hasn't worked. My newer onset ones, I found it worked quite well. And there's no proof to that one that I can see, but that's just what I found so far. So I don't tend to use it for somebody with... who's had diabetes for a long time now as a second line." — Physician, Ottawa*

Cost

- *"Having a drug plan will play an effect, also, to go into a second-line being that some of them will cost a lot more than others. So it's going to come into account in determining what your second line will be." — Physician, Ottawa*

- *"Well, I think it depends a lot on the patients. And again, it goes back to coverage, whether they're on open fee or a benefit plan or coverage, because if they can't afford the medication, they probably won't take it. I guess a lot of it is you sort of get a feel for the patient yourselves, too. I mean, some patients you might start insulin earlier if they don't have a drug plan." — Physician, Ottawa*

- *"Yes, sort of the same feeling. It depends if a patient's got insurance or whatnot. So I mean, given like your rich patient who has insurance, obviously I would take metformin first and then, second-line, I've started using the Januvia. It seems to be pretty good and very low... like no side effects. But that's very new so it's sort of new in the picture." — Physician, Ottawa*

- *"But there still are the occasional patients where for various reasons they can't afford anything else. They refuse to take insulin and whatever, and then you might go and push the dose further. But, the odd patient, you might be convinced that there's a benefit going higher, but usually not." — Diabetes specialist, Newfoundland*

- *"I wouldn't even consider them. A large bulk are clients, they have a federal health plan, so they don't even have coverage. So right away, those aren't even on the table, so you kind of default to the older therapies, regardless of the efficacy then. Just something to get the job done." — Nurse Practitioner, Ottawa*

Side Effects

- *"Well, again, there are a significant number, I think, of people that don't tolerate it. That get primarily GI side effects, and so we have to abandon and then you may not be able to get to the full two grams a day and you might be looking if they can only tolerate a partial dose or none, then you're going to go on to the next agent." — Physician, Halifax*

- *"Symptoms, as well, because I had one person whose hemoglobin A1C was at target, sugar's not too bad, but the ophthalmologist said you've got to get them on more medicine because of all the changes they were seeing in the eye." — Physician, Ottawa*

- *"I mean, if their kidney function is deteriorating, their GFR is going down; I mean, if their GFR goes down below 60, I would cut back on metformin to one gram a day, maximum. If it goes down to about 30, I would think about stopping metformin. Or if they're having side effects, then I might stop the metformin, depending on whether they're having a lot of GI side effects. But otherwise, if they're doing well, not having any contraindications taking metformin, I would continue indefinitely, as long as they didn't go over the A1C of less than 7 generally. Or if it's a high risk patient, sometimes you want the hemoglobin A1C to be a little bit lower." — Physician, Ottawa*

- *"GI side effects. Diarrhea, nausea mainly. Yes, those would be the high side effects in terms of whether it works. I think it would be tried for two or three months, and if there was an improvement in the A1C, then it would probably continue." — Diabetes specialist, Ontario*

- *"They won't have hypoglycemia, on a TZD. But if you start adding a sulfonylurea with metformin, then you run the risk that they could have a low sugar. So you need to know your patient pretty well because you want this patient going low. They deal with that. Are they elderly? Are they going to fall? You know what I'm saying?" — Nurse Practitioner, Ottawa*

Weight Gain

- *"And there's issues, as well, that it causes weight gain, and it is fat that's increasing insulin resistance. But I think we're probably creating a vicious circle, that should we put somebody on sulfonylurea, you're temporarily lowering the glucose, but a patient gains more weight, they get more insulin resistant, so their glucose starts to rise again, then you need to up the dose. So the natural history, just like the natural history on insulin, tends to be that the weight goes creeping upwards and you're always chasing your tail." — Diabetes specialist, Newfoundland*

- *"Well, I don't like either drug (glyburide and Diamicron) tremendously because both lead to a degree of weight gain, and this is one of the issues that you're trying to prevent, but they do offer better control." — Diabetes specialist, Ontario*

- *"Yeah, it's always the weight gain problem. Weight gain." — Physician, Halifax*

- *"But if you can present some of the side effects of the sulphonylureas — sometimes, too, like if they know they're going to gain weight or something, too — you can sometimes sort of "apple and the cart" sort of thing, that they don't want to gain weight, especially if they're usually hefty." — Physician, Ottawa*

Hypoglycemia

- *"There's also the issue of the increased risk of hypoglycemia, especially with the older agents. But there's always that it's cheap, like the older ones; glyburide and so on are cheap. And so just like metformin, the issue is cost. If the issue is a provincial formulary and the elderly and so on, then we're often forced into it." — Diabetes specialist, Newfoundland*

- *"And then hypoglycemia's always a concern, and particularly, say, in a client that's elderly, has renal failure, a seizure disorder, anything that would really precipitate another kind of event for that client if they had a low blood sugar. I'd say that's pretty good." — Nurse Practitioner, Ottawa*

Adverse Effects

- *"Well, the maximum dose is 2,500 milligrams a day, which is five tablets. Now that said, the adverse effects really go up as you increase the dose of metformin, so that 1,500 or 2,000 milligrams of metformin does almost the same job as 2,500 milligrams. And yet, as you get to the highest dosage, the maximal dosage, the adverse effects increase markedly. So we strive usually about two grams, depending upon the size of the patient, which is four tablets of metformin. And we will try this with lifestyle changes if their blood sugars are not too bad." — Nurse Practitioner, Ontario*

- *"And now, just in the last couple of weeks, there's been more and more reassuring data that the concern about increasing cardiovascular mortality probably isn't real. So my second line is generally the TZD."— Diabetes specialist, Newfoundland*

Ease of Use

- *"Once a day is great, if that's what you've got, if your medication is once a day, because again, they're on this whole group of things they have to do. So simplifying the regime, I think, is great. Or as [other participant's name] said, if you can make a combination drug that will do the job, again, that simplifies it." — Physician, Ottawa*

- *"Yes, I think early on, I don't think they know enough to prefer any one or another. And as they progress along, they begin to learn a little bit more about diabetes, either through other patients they talk to or [by] read[ing]. I think the agents that have the fewer side effects and ease of use is what they prefer…" — Diabetes specialist, Ontario*

- *"I mean, there are some patients who are very knowledgeable about their disease and the management of it, and they're not the ones that have the stroke and come to see me. So I think that patients want ease of use. So the simpler it is to take, again, a once-a-day formulation is going to be more popular to a patient than multiple daily dosing. And something with a lower risk of hypoglycemia is going to be more interesting to a patient than something that they have to worry about taking meals on regular time periods." — Nurse Practitioner, Halifax*

APPENDIX D: SAMPLE QUOTES FROM PATIENTS

The following quotes from patients with type 2 diabetes showcase the central themes observed in their discussion of second-line antidiabetes drugs.

Confidence in the Care Provider

- *"Trust the doctor." — Halifax*
- *"Oh, if you trust your doctor, you're not really crazy about taking another pill. But if he explains it to you and why he's doing this and if he's thinking another way, that's not too bad." — Ottawa*
- *"Well, I don't mind because I have great confidence in my doctor. And if this is his decision, then I will abide by it. And, you know, which I've done. I was really surprised to learn, and I think the statistic is, of all medications prescribed by doctors, I believe patients only take about 20%." — Halifax*
- *"My doctor's a professional, you know, so I have absolute faith in her." — Halifax*
- *"Well, this is it. I think we have confidence in our practitioners." — Halifax*
- *"My background is such that if the doctor prescribes something, you take it, you don't ask questions. They're doing this for your health. They're going to make you well. I'm attending with this one physician, that's very well-known in Canada. She's got an excellent reputation in the field, CRT, and she's been at the [name of health care agency] for many, many years. She'll prescribe something to me, she'll mention one thing that maybe this will reduce that thing, but it might send you to the bathroom a little more often. End of discussion. I've also got an excellent druggist. He will not send out a bottle that's been the first time to me without a two-page letter outlining all the possible side effects." — Ottawa*
- *"You know, my husband's really good about that and he sends a lot of government kind of things that come up, so we trust those kinds of things. But I guess he has the computer set up that when something comes up about diabetes and it comes through the Canadian Health Association, or I'm not sure which ones, he gets all those to automatically get fed through the computer." — Ottawa*
- *"I go to the Canadian Diabetic Association. And I also go to the Mayo Clinic. Any questions, I go to their website and just check things out about a lot of things." — Ottawa*
- *"I go to the pharmacist. I mean, they don't have time to go on and on and have a real private discussion for your own particular case, but very helpful." — Halifax*
- *"And a lot of times they [pharmacists] know... they appear to know a little bit more than your doctor about it." — Halifax*
- *"They've [pharmacists] been studying drugs longer than a doctor does, and I know that." — Halifax*
- *"If I'm still running into questions, I know three pharmacists really well, basically because they've been my pharmacists in the past, and I'll go to all of them and ask them what they think of that. Especially when you get an answer from your doctor like, well, I'm not really fussy about that one, I prefer this one. You know, so it's like, it's too big." — Ottawa*

Satisfaction With Care

- *"Well, I was fortunate enough to have a doctor that really informed me about the process of diabetes over the years, so I was not... I mean, I didn't feel anything particularly different when that happened, but I guess I was more relieved that there is a long-term process for me to stay healthy so I know that as long as I'm doing my part, as my ability to deal with my sugars, my body deal with my sugars decreases, then my doctor can assist me to counteract that." — Halifax*

- *"[Asked if worried about weight gain or hypo] Not a bit. I'm not in any way sensing any ill effects. As a matter of fact, I think I've managed to lose between 10 and 12 pounds since I was first diagnosed and it hasn't had any... In fact, the weight loss seems to help with the sugar levels. So, you know, I'm still working on it and every now and again I'll have a little relapse. I spoil myself occasionally." - Halifax*

- *"I think what it boils down to is that what alternative do we have? This is the best medication there is. We have access to it." — Halifax*

- *"Well, he sent me to a diabetic specialist and she met with him and I, we discussed what would be a good next step. And of course, over a couple of weeks I tried the Amaryl and it seemed to be working, so that's when we made the decision I'd be staying on it." — Halifax*

- *"She [family physician] discusses everything. Like, I just not that long ago went to the fourth metformin. She's okay, well, we can do this, you lose five pounds, we forget about the fourth one, and she lays everything out. She's an amazing doctor. I often have appointments of up to an hour with her." — Ottawa*

- *"That's a very common interaction I have with my doctor, because I read a lot, I study a lot. And we will discuss it and she will pull up and well, if you don't want to take this one, give me three months for the next visit, read this study, read this study, read this study and you'll see why I'm saying this. If we still don't agree, you're still number one of the team, so you pick what you do. But this is why I'm telling you to do it." — Ottawa*

- *"I'm good. I'm fortunate enough that my medical plan covers it because it's an expensive drug." — Halifax*

- *"And I was very good about keeping a log and I have a very good doctor and I test once a day, but different times during the day, and that's how he wanted to put it on. And now I'm on gliclazide, and it seems to be really good, because the last time I was there, I was 5.35 for that AB, whatever it is, the long-term test. So that's lower than 6 and he's very, very happy where I am right now." — Ottawa*

- *"I figure they'd find out just in the adverse side effects. I go back to the doctor and say, 'what are you doing to me?' But I feel great, so I'm just going ahead." — Halifax*

Fears

- *"I had a heart attack so they put me on all kinds of drugs. And it wasn't getting low enough, so they tried me on glyburide first, and that made me way too low. I only was on that for a month and, after, I was 3.3 for three days in a row; at the same time, I just got scared. I really got scared." — Ottawa*

- *"I just couldn't get sugars under control no matter what I did. It was really scary at first when they... well, he, my doctor wanted me, they first put me on the two slow-acting, the morning and the night one, and I was very, very scared of needles. And I remember getting it and having them in my hand and it took me about an hour to put it in myself because I was like, ugh, you know, like. Now it's just like... it's not even..." — Ottawa*

- *"Back then, I was anxious when it happened. Yeah. I was. Now I guess I would know ahead of time because I'm doing my own, you know. [Laughs]. You just kind of know this is not good." — Halifax*

- *"It's something that I'm concerned about. I carry sugar. I don't know about anybody else, but I know 10 or 15 minutes before the onset I can feel... I can feel it starting to change." — Halifax*

- *"I think my number one concern is going low because that happened a couple of times and it's not a pleasant place to be. But I am equally concerned about going high. I know in the long-term, it's dangerous for me, but in the short-term, going high is what depletes my energy. But there are certain risks, and the hypo is definitely a risk that you don't want to take." — Ottawa*

Frustration

- *"Oh, it's just frustrating. Like, it's embarrassing. I don't like to do it in front of other people. You know, like when we go away, I take my medications and I put them in my carry-on thing. I don't want anybody else to see it because the biggest thing they have for pills, then you fill it because you've got to have the vitamin B6 [which] helps you in the morning and all that kind of stuff. So, you know, like they're not prescription medications, but you're on them, and it just looks like... I feel like perhaps... I feel like I'm maybe, you know, what do you call it, a hypochondriac?" — Ottawa*

- *"I was very disappointed, very upset. Like I was doing something wrong, yeah, I was. Like I was doing something wrong and I couldn't figure out what I was doing wrong and very prepared to watch myself very closely. That's why I kept a log; because I was convinced that if it wasn't going to work, I wasn't going to take it." — Ottawa*

- *"Similar feelings. Feel like I'm disappointing. A total failure." — Ottawa*

- *"For me, it's more of what's going to screw up my work day, because if I'm going to be running to the bathroom all the time, or have no energy, or have a horrible headache, or whenever I'm going to be out for a couple of days, you know, and that's going to affect productivity and that." — Ottawa*

- *"My doctor quit. With short notice, and just disappeared. And then, so I had to use walk-ins. Luckily, there's a walk-in attached, so they had my file and now I have a doctor. I find that their focus is not my focus. You know, as you said, they're numbers. But when my numbers get to where they want them, I have the energy of a brand newborn baby kitten. I have no energy. I can't do anything. It's hard to be even interested." — Ottawa*

- *"I was not given any options about it. It was just this is step two and this is what we're going to do. And you could ask a question about the weight gain or anything else like that, but it was never a question that was going to change the course of the appointment." — Ottawa*

- *"I was told, 'This is what you're on. And I'll see you in six months.'" — Ottawa*

- *"I get ten minutes, if I'm lucky. I've spent longer with the receptionist. She takes my weight and my height." — Ottawa*

- *"I've got an appointment every December. Fifteen minutes." — Ottawa*

Uncertainty

- *"I started on the metformin and the glyburide — this goes back almost 15 years. And I'm still on them. But I'm also on a bit of a cocktail that I've been on for many years. I'm also taking gabapentin, atorvastatin, and Rimapril hydrochlorothiazide. I'm still not sure why I got the third one. And I have been on that cocktail for years. What the drugs are I'm on and what their purposes are, I don't know. She's not very good at telling me that sort of thing. She will hand you a prescription and so you see when three months is up." — Ottawa*

- *"Yeah, I was put on metformin and I was 33 years old, and I was never... I just took my drug, trusted. My doctor never told me anything. Never told me it was a fertility enhancer. My son is... my daughter's 21 and my son was 14, and now I have an 18-month-old boy. But then I was put on Diamicron... so I was put on first Actos. So that was two metformin in the morning and Actos. And then finally it was two metformin in the morning, two at night, and then an Actos. And then, now, it's like two metformin and two Diamicron and Actos, but my sugars are beautiful, never over 8 but... or never over 7, but all the drugs are causing me to gain weight. They shouldn't be, right?" — Halifax*

- *"I think I just wondered what the new pills were going to do to my body, because when I started metformin, taking five a day, there's awful side effects to it. I've taken it for eight years now and I know what the side effects are and I just wonder, does this new pill, how is it going to mix with my others and what side effects is it going to have?" — Ottawa*

- *"I cross-question everything now." — Halifax*

- *"I wish I knew more. Well, a lot about the side effects, really. What's going to be the long-term happening from taking this, any particular treatment for diabetes, whether it's the type of insulin or pill?" — Halifax*

- *"I think I differ with you on that. Medications are just chemicals devised by researchers. Look at the poor women that trusted thalidomide. That's just one example. Perhaps if they'd questioned at that time?" — Halifax*

- *"Sometimes when you look at it [Internet information] you say, 'Should I really be taking this?'" — Halifax*