The New England Comparative Effectiveness Public Advisory Council

An Action Guide for Type 2 Diabetes Management

Next Steps for Clinicians

February 2015

Completed by:

The Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Introduction

About ICER and CEPAC

The Institute for Clinical and Economic Review (ICER) is an independent non-profit health care research organization dedicated to improving the interpretation and application of evidence in the health care system. The New England Comparative Effectiveness Advisory Council (CEPAC) is one of ICER's two core programs. CEPAC is a regional body whose goal is to provide objective, independent guidance on the application of medical evidence to clinical practice and payer policy decisions across New England. Backed from a consortium of New England state health policy leaders, CEPAC holds public meetings to consider evidence reviews of a range of topics, including clinical interventions and models for care delivery, and provides judgments regarding how the evidence can best be used across New England to improve the quality and value of health care services. ICER manages the day-to-day operations of CEPAC as one of its core programs designed to translate and implement evidence reviews to improve their usefulness for patients, clinicians, payers, and policymakers.

About this Guide

This document is a companion policy guide designed to help clinicians treating patients with type 2 diabetes make use of the results from a recent ICER evidence review and meeting of the New England Comparative Effectiveness Public Advisory Council (CEPAC) on "Controversies in Type 2 Diabetes Management."

CEPAC held its meeting on type 2 diabetes management on October 29, 2014 in Providence, RI. During the meeting, CEPAC voted on the comparative clinical effectiveness and value of different management approaches, and explored how best to apply the evidence to practice and policy with a distinguished Policy Expert Roundtable of patient advocates, clinical experts, and policy leaders from across New England.

This guide is intended to provide clinicians with a series of action steps that can be taken to improve the efficiency and quality of care. The content provided here is based on the published evidence as well as best practices recommended from subject matter experts during the CEPAC meeting. This guide is for informational purposes only, and it is not designed to replace professional medical advice.

INDIVIDUALIZATION OF TREATMENT

1. Determine appropriate HbA1c target based on individual factors.

Diabetes care and treatment goals should be individualized to the patient as much as possible. The philosophy of diabetes management heretofore has been to bring patients to a specific HbA1c target of ≤ 7%. However, the drive for blood glucose levels less than 7% will not be appropriate for many patients. Treatment aims should always reflect a balance between the goals of reducing long-term adverse clinical events and managing hypoglycemia and other side effects of treatment.

As much as possible, individualize your patients' HbA1c goals

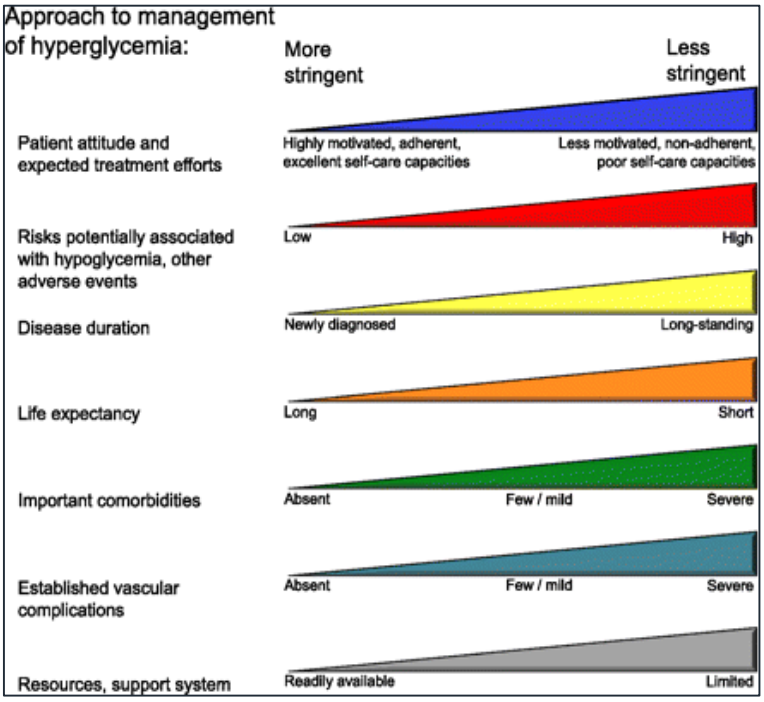
American Diabetes Association guidelines:

Population	A1c Goal
Patients with: Short disease history, long life expectancy, no heart disease	**<6.5%**
Standard	**≤7%**
Patients with: Long disease history, short life expectancy, comorbid conditions	**<8%**

Canadian Diabetes Association online tool to guide goal-setting.

Guidance from the ADA for setting A1c goals

From Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach



Patient preferences should inform decisions of treatment goals and pharmacotherapy choice. For many patients with type 2 diabetes, comorbid conditions are a major concern. For some, even a marginal increase in weight may require some patients to go back on blood pressure medication, complicating treatment regimens. Other patients may be unable to intervene independently to manage their hypoglycemia. It is important for physicians to explain the relative risks and benefits associated with different pharmacotherapy options in terms that are acceptable and understandable to patients, and develop HbA1c targets and other treatment aims with individual patient factors in mind. Involving patients in the decision-making process using tools such as those provided at right can help to increase engagement in treatment.

Tools to guide patient decision-making discussions:

- Medication Decision Aid from Mayo Clinic, a tool for supporting medication choice discussions that compares side effects, prices, administration, and other factors
- VA Guidelines for Involving Patients in Decision-Making

2. For patients requiring insulin, consider human insulin (NPH) as the initial choice instead of more expensive insulin analogs.

Most patients with type 2 diabetes can achieve equal levels of glycemic control with regular human insulin (NPH) or long-acting analog formulations, and some well-respected clinical organizations maintain most patients on NPH. Research demonstrates that NPH use does not result in higher levels of weight gain nor does it cause more adverse events, except for "nonsevere" hypoglycemia (i.e., symptomatic or nocturnal events that do not require third-party intervention) (ICER, 2014). Considering the evidence on clinical effectiveness and costs, CEPAC determined that human insulin offers high value compared to long-acting analog alternatives. Human insulin is potentially underutilized and clinicians should support its use in appropriate patients.

Prescription Guidelines

The guidelines listed below suggest starting patients on NPH insulin, except under special circumstances.

US Veteran's Affairs Guidelines: Long-acting analogs may be considered in patients treated with NPH who have frequent or severe nocturnal hypoglycemia.

CADTH (Canada) Guide to Prescribing Insulin recommends starting patients on NPH insulin over insulin analogs

NICE (UK) Guidelines recommend use of insulin analogs only in patients who:

- Need help with insulin injections from a caregiver or healthcare professional
- Have had repeated and unpleasant hypoglycemic episodes that significantly affect lifestyle
- Would otherwise need to have two daily insulin injections, in addition to other diabetes medications

NPH insulin is a reasonable first choice for most patients, but insulin analogs should be considered for patients with co-morbid conditions or other unique circumstances that make managing hypoglycemia more difficult. As outlined above, several organizations support initiating insulin therapy using NPH insulin. Frequent follow-up visits with patients to monitor adverse events can help clinicians decide if transitioning to an analog is appropriate. Nurse case managers, dieticians, diabetes educators, and community health workers play key roles in providing ongoing education, support, and monitoring for patients with type 2 diabetes. Additional patient education can help reduce the perceived concerns regarding hypoglycemia and adherence with NPH. The American Diabetes Association offers guidelines for minimum standards of diabetes self-education. Further materials for educating your patients on how best to maintain blood glucose levels while using NPH insulin are available on the following page.

Providing information about the risks and benefits of insulin and on how to avoid complications such as hypoglycemia can help support initial use of NPH insulin.

These links provide information to explain hypoglycemia and help patients manage it on their own	
Explaining Blood Glucose	A handout by the American Diabetes Association to share with patients that explains
Managing and Preventing Hypoglycemia	A handout by the Academy of Nutrition and Dietetics that provides information to help patients identify, treat, and prevent hypoglycemia
"What is low blood sugar?"	Patient resources for managing blood sugar from Lilly Diabetes
NICE academic detailing aid	This tool provides prescribing and medication optimization messaging for healthcare personnel to support the use o NPH insulin.
CADTH Guide to Starting and Adjusting Insulin for Type 2 Diabetes	This guide shares findings from the Canadian Agency for Drugs and Technologies in Health's review on evidence surrounding type 2 diabetes treatments. CADTH recommends NPH insulin as the first-line choice before insulin analogs.

Throughout New England, switching from analog to NPH would yield close to $1.7 million in cost savings for every 1,000 patients.

The lower cost of NPH insulin may be significant for some patients. Patients may be able to more easily afford their medications and remain adherent to treatment. On a system level, the cost savings could allow more funding for diabetes educators and self-management programs.

SECOND- AND THIRD-LINE MEDICATION OPTIONS

3. Consider the initial use of metformin and other high value options before more costly alternatives.

Nearly all patients requiring pharmaceutical treatment should be started on metformin as first-line therapy, and the use of metformin should be optimized before considering the addition of other options.

Second-line therapy with sulfonylureas is a reasonable choice. Though GLP-1 receptor agonists offer incremental clinical benefits related to reduced weight gain and incidence of hypoglycemia, the balance of the clinical benefits versus the high per-patient incremental cost make GLP-1 receptor agonists a "low value" second-line therapy compared to sulfonylureas (ICER, 2014). Evidence is inadequate to demonstrate clinical advantages of DPP-4 inhibitors over sulfonylureas. The table on the following page provides an overview of selected medication options, including their risks, benefits, and costs. For a comparison of the use, risks, benefits, and costs of sulfonylureas, GLP-1 receptor agonists, and DPP-4 inhibitors, see the table on the following page.

For most patients that have been unsuccessful with metformin alone, a sulfonylurea in combination with metformin represents the best value second-line treatment.

For patients who need additional therapy after metformin plus sulfonylureas, adding NPH insulin is a reasonable third-line choice. As with second-line treatment, GLP-1 receptor agonists offer incremental clinical benefits versus NPH insulin, benefits that will be of greater potential importance for some patients than others, yet the balance of the clinical benefits versus the high per-patient incremental cost make GLP-1 receptor agonists a "low value" third-line therapy compared to NPH insulin. Guidelines from the American Diabetes Association suggest that, for many patients requiring third-line treatment, insulin may be the best choice.

The VA policy provides an example of guidelines that suggest sulfonylureas as a second-line treatment option and insulin as a third-line option over the use of GLP-1 receptor agonists, except in select patient groups.

Prescribing Guidelines: U.S. Veterans' Health Administration

To receive a prescription for a GLP-1 receptor agonist, patients should meet the following criteria:

- Patient has type 2 diabetes
- Patient has not achieved desired HbA1c using combinations of > 2 oral hypoglycemic agents at maximally tolerated doses (except in cases on contraindication)
- Patient is not a good candidate for insulin

If a patient does not meet these requirements, a second-line regimen of metformin + sulfonylurea is recommended, except when contraindicated.

Source: VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives. GLP-1 Agonists (Exenatide, Liraglutide, Albiglutide) Criteria for Use.

Though GLP-1 receptor agonists are considered to be a low value second- or third-line treatment option for a majority of patients, a small subpopulation of patients may gain significant added benefit from GLP-1 receptor agonists and should be considered for therapy using this medication class.

The table below outlines the use, benefits, possible risks, and costs of select medications. Risks included represent the most notable adverse events. Dosing information is based on the usual effective dose and may vary between patients.

Characteristic	Sulfonylureas	GLP-1 receptor agonists	DPP-4 inhibitors
Brand and generic name(s)	*First generation:* chlorpropamide (Diabinese®), tolbutamide (Orinase®) *Second generation:* glipizide (Glucotrol®), glyburide (Micronase®), glimepiride (Amaryl®)	exenatide (Byetta®) exenatide extended-release (Bydureon®) liraglutide (Victoza®) dulaglutide (Trulicity®) albiglutide (Tanzeum®)	sitagliptin (Januvia®) saxagliptin (Onglyza®) linagliptin (Tradjenta®) alogliptin (Nesina®)
Administration	Oral tablet	Subcutaneous Injection	Oral tablet
Use and effects	Typically taken 20 – 30 minutes before mealtime for optimal blood glucose control	Taken weekly, twice daily before mealtimes, or once daily to control blood glucose levels	Taken once daily with or without food to control blood glucose levels
Usual effective dose	tolbutamide: 500mg – 3000mg chlorpropamide: 100mg – 500mg glyburide: 1.25mg – 5mg glimepiride: 1mg – 8mg glipizide: 5mg – 10mg	exenatide (extended-release): 2mg weekly exenatide (immediate-release): 10mg – 20mcg twice daily liraglutide: 1.2mg – 1.8mg once daily	linagliptin: 5mg once daily sitagliptin: 100 mg once daily saxagliptin: 5mg or 2.5 mg once daily
Main mechanism of action	Lower blood glucose by stimulating production of insulin by the pancreas.	Slow digestion and lower blood glucose by increasing insulin secretion in presence of elevated glucose levels and suppressing glucagon secretion.	Lowers blood glucose by preventing the degradation of incretin hormones by DPP-4 enzymes, thereby increasing insulin secretion and decreasing the release of glucagon from the pancreas
Benefits	Generic versions available	Low risk of hypoglycemia when used as monotherapy; weight loss	Neutral effect on weight; low risk of hypoglycemia when used as monotherapy
Potential risks/most notable adverse events	Hypoglycemia, weight gain, heartburn, nausea, cardiac events	Nausea, vomiting , diarrhea; may be associated with pancreatitis	Upper respiratory infection, nasopharyngitis, headaches; may be associated with pancreatitis
Price for 30 days of treatment (based on average wholesale price (AWP) estimates)	**$55**	**$233**	**$326**

Micromedex Healthcare Series. RED BOOK® Online. Greenwood Village, CO: Truven Health Analytics, 2014. http://truvenhealth.com/. Accessed May, 2014.

4. **Develop treatment decisions with a consideration of the psycho-social context in which medications are being used. Integrated health care teams are essential to providing comprehensive management of the condition and ensuring that different treatment approaches are feasible given each patient's unique circumstances.** For many patients, the disease will not be controlled and the treatment goals will not be achieved without first addressing the underlying issues that affect an individual's ability to maintain a healthy lifestyle, access medication, and adhere to a complicated treatment regimen that can often be costly. The resources below can help you to better understand the psychosocial contexts in which your patients manage their disease and to develop treatment plans accordingly.

These resources can help you to assess the individual needs of your patients:

CDC Barriers to Being Active Quiz	Use this quiz to assess your patients' barriers to increasing physical activity to provide them with resources they need
Delivering Culturally Competent Care	This online course focuses on strategies for managing type 2 diabetes in diverse populations (CME eligible in CT, RI)
ADA clinical practice recommendations	ADA clinical practice guidelines uggest assessing patients' attitudes about diabetes; expectations of management; mood; quality of life; available resources; and psychiatric history.

5. Build health care teams that include nurse case managers, diabetes educators, pharmacists, and community health workers (CHWs) to help address patient needs. Adopting multi-disciplinary care teams allows more opportunities to reach patients outside of the practice setting to increase education and to better engage patients in their treatment choices. Comprehensive health care teams are also better equipped to intervene early when there are issues with treatment, thereby improving patient adherence. For example, some patients are unable to test blood sugar levels multiple times a day so are noncompliant to treatment regimens that require multiple daily injections and more frequent monitoring schedules. Nurse case managers and CHWs in particular can better account for the psycho-social context in which medications are being used and determine the feasibility of different management approaches given each patient's unique circumstances.

These resources can assist in the implementation and development of team-based care programs.	
National Diabetes Education Program: Practice Team-Based Care	Tools and resources for developing an effective health care team, including: a) examples of care team professionals and their distinct roles; b) steps for developing high-performance health care teams; c) defined goals and specific measurable, operational objectives for team building; and d) additional resources and references.
Agency for Healthcare Research and Quality: Implementing Care Teams	A training module designed to help health care professionals implement team-based care approaches in primary care and other practice settings.
American Association of Diabetes Educators: Provider Information	Information for physicians and other clinicians on diabetes self-management training and medical nutrition therapy and how to make referrals for these services and improve access to education for individuals with diabetes.
Program Example: Project Dulce, Scripps Health	Project Dulce is a diabetes care and education program that relies on teams including a certified diabetes educator, medical assistant, and dietician, who work with the patient's primary care provider. The program uses socio-cultural research to tailor care to a variety of communities.

6. Consideration of pharmacotherapy for patients with type 2 diabetes should be only one component of a broader management plan that emphasizes lifestyle changes and behavioral support.

Materials to facilitate patient discussion and education

Helping patients understand strategies to improve their lifestyle habits is essential to supporting their management of diabetes.

Explain complications:

- Patient Information on Complications, this guide from the ADA uses plain language to cover the most common complications of diabetes

Discuss healthy eating habits:

- Talking with Patients about Weight Loss: Tips for Primary Care Providers: Tips for discussing weight from the NIDDK
- Healthy eating resources from ChooseMyPlate.gov
- Healthy Eating on a Budget from the American Dietetic Association
- MyFoodAdvisor, American Diabetes Association
- Healthy Eating Tip Sheets from the Dairy Council of California
- Tools and calculators for measuring glucose and carbohydrate intake
- A guide to carbohydrate counting to help patients manage blood glucose levels

Explain the importance of exercise:

- Encouraging Patients to Be Physically Active: What Busy Practitioners Need to Know, from the American Diabetes Association
- Types of Activity: Suggest a variety of activities to your patients, and be clear about how often they should do each activity
- Diabetes and Physical Activity: Your Exercise Prescription: A useful resource from the Canadian Diabetes Association
- Visit the Canadian Diabetes Association website for more resources and patient education materials

The CEPAC report addresses only a subset of the diabetes problem. Type 2 diabetes is often related to preventable causes, and the greatest improvements to patient outcomes may be driven by changes to lifestyle. Decisions of medication choice should be considered within a broader treatment strategy that prioritizes **patient education, diet, and exercise**. Education plays an essential role in helping patients understand their disease, the appropriate level of activity and carbohydrate intake, and consequences of diabetes if left uncontrolled.

*More patient education handouts available from the **American Diabetes Association**, the **American Association of Diabetes Educators,** and **Learning about Diabetes** (English and Spanish versions available)*

6. The clinical research community should support the development of evidence and future research in the following areas:

- **Further study of insulin pumps and continuous glucose monitors** is needed to understand if certain patient subpopulations with type 2 diabetes may benefit from these technologies. For future research to be relevant, additional regulation may be required from the FDA since at present, devices change and are upgraded so frequently that conducting meaningful long-term studies is impossible. CEPAC members recognized the challenge to developing a robust evidence base for devices, as it is more difficult to perform a blinded study and there may be issues regarding confounding.

- **Further research is needed to understand the heterogeneity of treatment effects, and an identification of patient subpopulations** whose risk for significant hypoglycemia should lead to initial treatment with analog insulin, GLP-1 receptor agonists, or DPP-4 inhibitors. Many important patient subpopulations are excluded from clinical trials, so little is known at present about treatment effects in patient groups that are not well-studied.

- **The research community should develop study designs that reflect patient preferences and analyze treatment regimens that are feasible for patients to maintain.** Further studies should also be framed around more patient-centered questions, like the percent of patients that achieve reductions in HbA1c levels without experiencing an adverse event. Conceptualized this way, research will more helpfully inform treatment decisions by addressing the questions that matter most to patients.

- **Additional long-term studies are also needed that analyze primary rather than intermediate outcomes.** Patient and clinical communities want to know the effect new medications have on mortality, myocardial infarction, stroke, and other long term complications of diabetes (e.g., retinopathy, neuropathy). Evidence on long-term outcomes exists for sulfonylureas, but is still lacking for newer medications.