Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Diabetes Treatment Overview***
-August 2017-

Background:
Diabetes mellitus is the seventh leading cause of death in the United States with a point-prevalence in 2014 of 29.1 million persons living with the disease.[1] Type 2 diabetes is by far the leading subtype. Health disparities related to diabetes in Indian Country include not only a substantially higher prevalence among both adults and adolescents but also increased morbidity and mortality compared to the general population.

Discussion:
Diabetes treatment goals include a reduction in both microvascular and macrovascular complications as well as death from all causes. Intermediate, or so-called "surrogate" outcomes, include measureable declines in hemoglobin A1c, weight, and systolic blood pressure. Cardiovascular complications of diabetes result from a complex milieu of pro-inflammatory variables linked both directly and indirectly to insulin resistance. The effectiveness of multiple anti-hyperglycemic agents to reduce both microvascular and macrovascular complications have been demonstrated in studies of older and newer agents. Generally missing are well-designed, large, head-to-head studies adequately powered to measure the comparative effectiveness of the different agents, especially the newer ones, in improving clinical outcomes.

It is important to note that the basis of diabetes treatment for all patients is lifestyle therapy. This includes nutrition and behavioral support, regular physical activity, weight management, tobacco cessation, and good sleep hygiene.

Findings:
During the August 2017 meeting, the NPTC reviewed recent guidelines from the American Diabetes Association (ADA), the United Kingdom's National Institute for Health and Care Excellence (NICE), the American Association of Clinical Endocrinologists (AACE), and the American College of Physicians (ACP).[3-6]

The current ADA treatment recommendations represent the "patient centered approach" advocated in its joint position statements published in 2012 and 2015 with the European Association for the Study of Diabetes.[2-3] The 2012 statement was less prescriptive than prior recommendations. This was prompted primarily due to an increasing number of available anti-hyperglycemic drugs and growing uncertainty among providers regarding the proper selection and sequence of medications. Because of an identified lack of comparative effectiveness research and unclear impact on long-term outcomes, an individualized treatment strategy without a specified hierarchy of meds has been advocated. In its 2015 position statement, the ADA identified the need for studies of the cardiovascular impact of the various newer glucose lowering therapies.[3] It also noted the anticipated publication in 2020 of the comparative effectiveness study, The Glycemia Reduction Approaches in Diabetes (GRADE), currently underway to assess long-term outcomes of multiple agents after failure of metformin monotherapy.

Various glycemic control targets are advocated by current guidelines and range from a hemoglobin A1c of 6.5 to 8.0% depending on patient characteristics. Individualized targets are advocated, with more stringent goals generally reserved for younger patients, those newly diagnosed without significant comorbidities, and those least at risk of significant hypoglycemia. Less stringent targets are indicated for older persons with significant comorbidities, history of severe hypoglycemia, those with limited life expectancy, and those with longstanding diabetes that has been difficult to control.

The ADA stratifies recommendations for the initiation of therapy based on the level of the hemoglobin A1c.[3] Metformin monotherapy is recommended for those with a hemoglobin A1c value less than or equal to 9.0% whereas dual therapy with metformin and a second line agent is recommended for those with an initial hemoglobin A1c of 9.1 to 9.9%. For those with an initial hemoglobin A1c over 10.0%, consideration

of combination injection therapy is advocated, such as basal insulin plus either rapid acting insulin or a glucagon-like peptide-1 (GLP-1) receptor agonist. Quarterly reassessment with intensification of therapy is recommended for those not at goal.

Dual therapy is warranted for those who fail to meet an appropriate glycemic control target with metformin monotherapy following a period of initial treatment.[3] Dual therapy consists of metformin plus one of a number of second-line agents including a sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium-glucose co-transporter 2 inhibitor, GLP-1 receptor agonist, or basal insulin. According to the ADA guideline, there is no hierarchy of preference among these agents and the choice of agent should be based on individual patient and disease-specific factors. For those not meeting their glycemic target at three months, triple therapy is recommended.

Triple therapy consists of metformin plus any two of the other agents with the exception of a combination of a DPP-4 inhibitor and GLP-1 agonist.[3] Again, there is no hierarchy of preference among the agents and choice should be individualized to the patient. For those still not meeting their goal at three months, combination injection therapy is advocated. According to the ADA guideline, combination injection therapy consists of metformin plus basal insulin and either pre-prandial rapid acting insulin or a GLP-1 receptor agonist or alternately, a switch from basal to pre-mixed insulin. If goals are still not met, basal-bolus or pre-mixed insulin three times daily is recommended. In deference to the complexity of treatment regimens and the resulting impact on medication adherence, the ADA advocates discontinuation of oral anti-hyperglycemic medications, with the exception of metformin, for those patients on combination injection therapy.

The NICE and AACE guidelines, also released in 2017, take a similar approach to medication management, with the exception that in the AACE guideline, specific treatments are ordered according to a recommended hierarchy of use based on expert consensus.[4-5]

Following a systematic review of the comparative effectiveness and risks of the various oral agents for the treatment of Type 2 Diabetes, the ACP updated its guidelines with the recommendation, based on strong evidence, to prescribe metformin when medication is needed for glycemic control.[6] Based on weak evidence, a combination of metformin and any other oral agent was recommended (when needed for better glycemic control), considering individual medication characteristics.

Conclusions:

A variety of drugs are available with similar efficacy for glycemic control and a range of both side effects and effectiveness for short- and long-term clinical outcomes. There is limited clinical trial comparison data to support superiority, especially among the newer agents. Most guidelines do not support a hierarchy among second and third line medication options. Contemporary guidelines do advocate individualized glycemic control targets and treatment strategies as well as a step-wise approach to therapy. Finally, metformin is both the best initial treatment for Type 2 Diabetes and should optimally be included in all combination treatment plans, except when contraindicated or not tolerated.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References:

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