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Indian Health Service National Pharmacy and Therapeutics Committee Insulin Resistance and Prediabetes NPTC Formulary Brief February Meeting 2017

Background:
The National Pharmacy and Therapeutics Committee has not previously reviewed medications for prediabetes or insulin resistance in metabolic syndrome. The National Core Formulary (NCF) currently has the following pharmacologic medications; metformin, bupropion, naltrexone and topiramate as stand alone agents (reviewed previously under other disease and pharmacologic reviews). As a result of this clinical review, no changes were made to the NCF. Metformin remains a preferred pharmacologic treatment recommended by national guidelines for prediabetes[1-2].

Discussion:
In the United States, 1 in 3 people have prediabetes but only 11% have been diagnosed. Of patients with prediabetes, 70% will develop type 2 diabetes mellitus (T2DM)[3]. There are no classic symptoms evident with insulin resistance and prediabetes however people over the age of 45 or those overweight or obese who have one or more risk factors for prediabetes should have a HgA1c, fasting plasma glucose (FPG) or oral glucose tolerance test (OGTT) performed[1-4]. Risk factors for insulin resistance include excess weight, physical inactivity, waist circumference >40 inches for men and >35 inches for women, ethnicity, hormones, steroids, sleep disorders and cigarette smoking[4]. Risk factors for prediabetes include physically inactive, parent or sibling with diabetes, ethnicity (including American Indians and Alaskan Natives (AI/AN)), gestational diabetes, uncontrolled hypertension, low HDL (<35mg/dL), polycystic ovary syndrome, obesity, acanthosis, or history of cardiovascular disease[4].

The goals are to prevent or delay progression to T2DM and reduce complications through glucose lowering and weight loss[1-2]. The American Diabetes Association (ADA) recommends diet, physical activity and behavior health therapy with a goal of >7% weight loss in patients with prediabetes with a body mass index (BMI) of 25 to 26.91. In those with a BMI of 27 to 29.9, the recommendation is diet, exercise, behavior therapy and pharmacotherapy, specifically metformin1. In those with a BMI of >30, recommendations include the above plus consideration for metabolic surgery1. The American Association of Clinical Endocrinologists (AACE) recommends intensive lifestyle management (medical nutrition therapy, physical activity, tobacco avoidance, limited alcohol consumption, adequate sleep and stress reduction) with a weight loss goal of 5-10%2. Pharmacologic therapy is recommended after 3 to 6 months in those not achieving improvement with lifestyle management2. An anorexient or antidiabetic agent with weight loss properties could be considered[2]. The 2013 American Heart Association / American College of Cardiology / The Obesity Society Guidelines for the Management of

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Overweight and Obesity in Adults suggest that weight loss between 2.5 to 5.5 kg sustained for >2 years can reduce the risk of developing T2DM by 30-60%[5].

Findings:
Non-pharmacologic therapy or lifestyle interventions such as diet, physical activity and behavior health therapy have been shown to be effective in preventing or delaying T2DM[1-2]. The Diabetes Prevention Program (DPP) was a four year, randomized controlled trial (RCT) involving a diverse ethnic population (including AI/AN) with a high risk of developing T2DM. The DPP contained three arms comparing intensive lifestyle interventions, metformin 850mg BID with standard lifestyle recommendations, and placebo with standard lifestyle recommendations[6]. The incidence of T2DM was 58% lower in the intensive lifestyle group vs. placebo (95% CI: 48-66%) and 39% lower vs. metformin (95% CI: 24-51%)6. T2DM incidence was also 31% lower with metformin vs. placebo (95% CI: 17-43%)[6]. Two long-term DPP follow-up studies of 10 and 15 years showed that delaying the development of T2DM could be sustained with lifestyle interventions and metformin[7].

Several pharmacological therapies have been evaluated in the prevention or delay of T2DM, including medications indicated for treatment of diabetes and obesity. They primarily have the benefit of weight loss, with the exception of pioglitazone. In ACT NOW trial, pioglitazone demonstrated significantly lower incidence of T2DM over placebo, 2.1% in pioglitazone vs. 7.6% in placebo (HR 0.28, 95% CI: 0.16 to 0.49, $p<0.001$) despite significant weight gain over placebo ($p<0.001$)[8]. The STOP NIDDM trial was a European trial evaluating acarbose, an alpha glucosidase inhibitor, in preventing the development of T2DM[9]. The results indicated that acarbose reduced development of T2DM by 25% (HR 0.75, 95% CI: 0.62-0.9, $p=0.0015$) and increased reversion of IGT back to normal glucose tolerance ($p<0.0001$)[9].

Several glucagon-like peptide 1 (GLP1) receptor agonists have been shown to significantly reduce weight over placebo[10-11]. Effects on glycemic control in obese patients have also been studied in liraglutide and exenatide. A 2015 RCT evaluated liraglutide 3mg with placebo, along with lifestyle intervention in both study arms, in patients with prediabetes or at high risk of developing prediabetes (overweight with 1 risk factor or obese)[10]. Liraglutide significantly reduced both weight (−5.6 kg, 95% CI: −6.0 to −5.1, $p<0.001$) and HgA1c vs. placebo (-0.23, 95% CI: -0.25 to -0.21, $p<0.001$)10. A RCT comparing lifestyle intervention plus exenatide 10ug BID or placebo reported a significant but modest 3.3% reduction in mean body weight (-3.5 kg weight loss) but was unable to demonstrate significant reductions in glycemic control (i.e., HgA1c, FPG, OGTT) over placebo.

In addition to antidiabetic agents, anorexiants have been evaluated for their effects on glycemic control[12-15]. The XENDOS study evaluated orlistat for prevention of diabetes in obese patients and demonstrated (in addition to significant weight loss) that orlistat reduced the incidence of T2DM compared to placebo by 37% (HR 0.63, 95% CI: 0.46 to 0.86, $p<0.0032$). This was primarily attributed to patients with IGT at baseline[12]. Those with normal glucose tolerance did not demonstrate significant changes in T2DM incidence between groups. Lorcaserin, another anorexiant, demonstrated significant reductions in FPG and HgA1c compared to placebo in the BLOOM trial, however this trial was not designed to evaluate T2DM outcomes[13]. Neithercombination medications phentermine/topiramate or bupropion/naltrexone demonstrated significant changes in FPG over placebo[14-15].

Conclusions:
The DPP showed that intensive life style modifications, including diet and exercise reduced/delayed the progression to T2DM significantly more than metformin or placebo with standard lifestyle recommendations. Both ADA and AACE guidelines recommend weight loss in the treatment of prediabetes, and overweight (with >1 prediabetes risk factors) and obese patients should be encouraged to achieve >5% weight loss to decrease/delay T2DM through intensive lifestyle management. There are currently no FDA-approved medications for prediabetes. Patient-specific factors should be considered when selecting pharmacotherapy for weight loss as safety profiles vary between agents.

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

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Indian Health Service
National Pharmacy and Therapeutics Committee
SGLT2 inhibitors
NPTC Formulary Brief
February Meeting 2017

Background:
The IHS National Pharmacy & Therapeutics Committee (NPTC) reviewed the class of sodium-glucose co-transporter 2 inhibitors (SGLT2i) at the February 2017 meeting. Prior to this, the NPTC performed an initial review of SGLT2i in February 2014 although the evaluation included only canagliflozin and dapagliflozin and neither were added to the National Core Formulary (NCF). As a result of the clinical and pharmacoeconomic evaluation in February 2017, the NPTC did not add any SGLT2i agents to the NCF.

Discussion:
The SGLT2i class of medications currently include canagliflozin, dapagliflozin and empagliflozin. These medications produce anti-glycemic effects through reduction of blood glucose via increased urinary glucose excretion1. All SGLT2i are approved by the Food and Drug Administration (FDA) for the treatment of type 2 diabetes mellitus (T2DM). Unlike other anti-diabetic agents, SGLT2i ability to lower glucose levels is independent of insulin and their use is rarely associated with hypoglycemia.

Randomized, controlled trials report that SGLT2i reduce A1c values on average from 0.5-0.7% (versus placebo) although A1c reductions have been noted from 0.4-1.1% depending on baseline levels. Direct comparisons of SGLT2i to active comparator treatments (metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, insulin) yielded modest, non-significant A1c reductions for SGLT2i of 0.06-0.13%[2-5] .

SGLT2i offer benefit beyond that of glycemic control, most notably with reductions in body weight and blood pressure. Several meta-analyses report weight loss (versus placebo) ranging from 1 to 3 kilograms which appears to be both sustained and independent of dose[5-7]. Compared with placebo, use of SGLT2i demonstrated a significant loss of body weight (-2.99 kg, 95% CI: -3.64 to -2.34) following 1 and 2 years of use[5]. Additionally, no significant differences in weight loss exist between the SGLT2s[7]. Reductions in blood pressure range from -2 to -6 mmHG for systolic blood pressure and -1 to -3 mmHG for diastolic blood pressure[6,7]. The exact mechanism for SGLT2i-associated lowering of body weight and blood pressure remains unknown but is theorized to relate to their osmotic, diuretic effects. SGLT2i are primarily indicated in T2DM patients with estimated Glomerular Filtration Rate (eGFR) of >60 ml/min. Canagliflozin and empagliflozin may be used in patients with eGFR <60 ml/min but >45 ml/min, however lower doses of canagliflozin are recommended. The SGLT2i are contraindicated in both patients with eGFR <45 ml/min and patients with type 1 diabetes mellitus. Prior to SGLT2i initiation, kidney function should be assessed at baseline and periodically during SGLT2i treatment.

The most common adverse events reported with SGLT2i include genital and urinary tract infections (UTI) and hypotension. All SGLT2i are associated with significantly higher rates of mycotic genital infections[6] (Odds Ratio: 4-6 versus placebo) while only dapagliflozin was found to have significantly more UTIs and genital mycotic infections than placebo[9]. A safety concern of serious UTIs requiring hospitalization has issued by the FDA. Due to the diuresis with SGLT2i, hypotension is a concern in older patients or patients receiving concomitant antihypertensive agents. Additional safety concerns have been published by both the FDA and Health Canada regarding the association between SGLTs and acute kidney injury[10] (canagliflozin, dapagliflozin), diabetic ketoacidosis[11, 12] (SGLT2s), bone fractures[13, 14] (canagliflozin) and amputations[15] (canagliflozin).

In December 2016, empagliflozin received an additional FDA approval for risk reduction of cardiovascular mortality in adults with T2DM and established cardiovascular disease. This indication resulted from the EMPA-REG trial[16], an international, post-marketing cardiovascular safety study (n=7020). The trial compared empagliflozin to placebo in patients with T2DM and established cardiovascular disease (secondary prevention) who were receiving standard care.

The primary outcome in the EMPA-REG trial was a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI) and nonfatal stroke. It was found to be statistically significantly reduced by 14% (Hazard ratio (HR): 0.86, CI 95%: 0.74-0.99, p=0.04 for superiority) with a number needed to treat of 63, over 3.1 years of treatment with empagliflozin. No differences in the primary outcome were noted between the two doses of empagliflozin (10mg, 25mg). Lower rates of cardiovascular death (HR 0.62, CI:0.49-0.77, p<0.001) and death from any cause (HR 0.68, CI: 0.57-0.82, p<0.001) contributed significantly towards the primary outcome results as neither MI and stroke rates differed from placebo.

Although EMPA-REG is the only SGLT2i cardiovascular trial to date to report statistically significant reductions in cardiovascular mortality, at least one analysis suggests this may be a class effect. A 2016 meta-analysis of 71 studies reported statistically significant reduction in all-cause mortality, cardiovascular mortality and MI, but not stroke. After removing the cardiovascular outcomes trials (i.e., EMPA-REG), no differences were noted among SGLT2i[17]. The remaining cardiovascular safety studies, CANVAS (canagliflozin) and DECLARE (dapagliflozin), should be completed in 2017 and 2019 respectively and will provide clarity on a potential class effect and the role of SGLT2i in primary and secondary prevention.

The 2017 American Association of Clinical Endocrinologists / American College of Endocrinology recommend SGLT2i as potential second- or third-line therapeutic options, after metformin. The 2017 American Diabetes Association guidelines also recommend SGLT2i as second-line agents, alongside 5 other anti-diabetic classes, when dual therapy is required. Metformin remains the preferred initial agent. A section was added with the recommendation to consider empagliflozin or liraglutide (when added to standard care) in T2DM patients with established cardiovascular disease to reduce mortality risk.

Findings:
The SGLT2i represent a novel, therapeutic addition to the current armamentarium of medications for the management of T2DM. In general, contemporary diabetic guidelines recommend SGLT2i as adjunctive therapy with metformin when necessary. In addition to their modest glucose-lowering effect, SGLT2i offer additional, favorable effects including weight loss and blood pressure reductions, and at least one SGLT2i has demonstrated a reduction in cardiovascular risk to date. The NPTC will collectively evaluate multiple anti-diabetic pharmacotherapy classes at the August 2017 NPTC meeting.

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

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