



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Insulin Resistance and Prediabetes
-February 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 prediabetes¹⁻².

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) performed¹⁻⁴. 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 smoking⁴. 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 disease⁴.

The goals are to prevent or delay progression to T2DM and reduce complications through glucose lowering and weight loss¹⁻². 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 anorexiant or antidiabetic agent with weight loss properties could be considered². The 2013 American Heart Association / American College of Cardiology / The Obesity Society Guidelines for the Management of 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 T2DM¹⁻². 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 recommendations⁶. 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 metformin⁷.

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 T2DM⁹. 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 placebo¹⁰⁻¹¹. 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, anorexiant have been evaluated for their effects on glycemic control¹²⁻¹⁵. 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 baseline¹². 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 outcomes¹³. Neither combination medications phentermine/topiramate or bupropion/naltrexone demonstrated significant changes in FPG over placebo¹⁴⁻¹⁵.

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.

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](#).

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