

# Improving Insulin Sensitivity: A Review of New Therapies

**MARY K. RHEE, MD**

Emory University School of Medicine  
Department of Medicine  
Division of Endocrinology, Metabolism, and Lipids  
Atlanta, Georgia

**GUILLERMO E. UMPIERREZ, MD**

Emory University School of Medicine  
Department of Medicine  
Division of Endocrinology, Metabolism, and Lipids  
Atlanta, Georgia

Insulin resistance is a state of impaired insulin action in insulin-dependent tissues—liver, muscle, and fat tissues. Impaired insulin action results in a reduction in insulin-stimulated glucose uptake and impaired insulin-mediated suppression of hepatic glucose production and adipocyte lipolysis. Insulin resistance may result from a disruption in any step of the insulin-signaling cascade. Defects in insulin signaling have been demonstrated in association with clinical predictors of insulin resistance, such as obesity, lack of physical activity, and a family history of type 2 diabetes mellitus. Weight loss and physical activity have been shown to improve insulin sensitivity in patients with diabetes. For many years, metformin and thiazolidinediones were the only pharmacologic treatments available that targeted insulin resistance; however, new classes of drugs, including the incretin analogs, dipeptidylpeptidase (DPP)-4 inhibitors, and endocannabinoid inhibitors, have been discovered. Incretins are intestinal hormones that are released in response to nutrient ingestion to stimulate insulin secretion by the  $\beta$ -cells of the pancreatic islets. Incretin analogs improve insulin secretion and insulin sensitivity and promote weight loss. DPP-4 inhibitors block DPP-4, an enzyme that degrades the endogenous incretin hormone glucagon-like peptide-1. DPP-4 inhibitors stimulate insulin secretion, inhibit glucagon secretion, and increase postmeal insulin sensitivity, but they do not appear to promote weight loss. Pharmacologic blockade of CB<sub>1</sub> receptors with endocannabinoid inhibitors has been shown to reduce food intake, promote weight loss, and increase adiponectin levels. These treatments may not only improve glycemic control but also offer the potential for additional metabolic and cardiovascular benefits. (*Clinical Cornerstone*. 2008;9[Suppl 2]:S28–S38) © 2008 Elsevier.

The epidemic of type 2 diabetes mellitus (DM) continues unabated, affecting >20 million Americans<sup>1</sup> and ~200 million people worldwide.<sup>2</sup> The burden of diabetes and its complications weighs not only on the affected individuals and their families but also on the health care system and its providers. Research has led to a substantial increase in the number of available pharmacologic treatment options over the past decade. These treatments have not reversed or stopped the progressive course of the disease, but they have helped slow disease progression and reduce the risk of complications by targeting the underlying pathophysiologic mechanisms of the disease—impaired insulin secretion due to  $\beta$ -cell dysfunction or loss,<sup>3</sup> and insulin resistance.<sup>4</sup> These mechanisms are the focus of this article.

## MECHANISMS OF INSULIN RESISTANCE

Insulin resistance is a state of impaired insulin action in insulin-dependent tissues—liver, muscle, and fat tissues.<sup>5</sup>

This impaired insulin action results in a reduction in insulin-stimulated glucose uptake in muscle and adipose tissue and impaired insulin-mediated suppression of both hepatic glucose production and adipocyte lipolysis. At the cellular level, insulin resistance may result from a disruption in any step of the insulin-signaling cascade, starting with the insulin receptor (IR),<sup>6</sup> followed by IR substrate (S)-1 or IRS-2, phosphoinositol-3-kinase (PI3K),<sup>7</sup> protein kinase B (or phosphokinase B [PKB]/AKT), phosphoinositide-dependent kinase (PDK)-1, and glucose transport.<sup>4,8–10</sup> Defects in insulin signaling have been demonstrated in association with important clinical predictors of insulin resistance, such as obesity, lack of physical activity, and a family history of type 2 DM (genetic predisposition). For example, insulin-resistant individuals who are obese or have a family history of type 2 DM have been shown to have decreased activation of IRS-1<sup>11,12</sup> and consequent reductions in insulin-

stimulated glucose transport,<sup>13,14</sup> all of which can be caused by increased levels of free fatty acids,<sup>8,15,16</sup> intracellular lipid content,<sup>17,18</sup> or mitochondrial dysfunction.<sup>8</sup> Modulators of the insulin-signaling pathway, including adenosine monophosphate (AMP)-activated protein kinase (AMPK),<sup>19</sup> inflammation,<sup>20</sup> adipokines (adipocyte-specific hormones, such as free fatty acids),<sup>15</sup> tumor necrosis factor- $\alpha$ ,<sup>21</sup> leptin,<sup>22</sup> resistin,<sup>23</sup> and adiponectin (an adipocyte-derived cytokine with important insulin-sensitizing effects)<sup>24</sup> also may play an important role in the development of insulin resistance.

### KEY POINT

**Insulin resistance is a state of impaired insulin action in insulin-dependent tissues—liver, muscle, and fat—with a consequent reduction in insulin-stimulated glucose uptake in muscle and adipose tissue and impaired insulin-mediated suppression of hepatic glucose production and adipocyte lipolysis.**

## ESTABLISHED TREATMENTS FOR INSULIN RESISTANCE

### Lifestyle Modifications

Weight loss and physical activity are mainstays of diabetes management.<sup>25</sup> Both aerobic exercise and resistance training have been shown to improve insulin sensitivity in patients with diabetes<sup>26,27</sup> by increasing glucose transport into muscle.<sup>27,28</sup> Similarly, weight loss is associated with an increase in insulin sensitivity,<sup>29</sup> possibly by activating AMPK and restoring adipokine levels toward those associated with better insulin sensitivity.

### Metformin

The improvement in diabetes control associated with metformin is predominantly due to its ability to reduce insulin resistance by increasing peripheral glucose utilization (mainly glucose uptake into muscle and glycogen synthesis) and decreasing hepatic gluconeogenesis<sup>30,31</sup> via LKB1-dependent<sup>31</sup> activation of AMPK,<sup>32,33</sup> with

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downstream increases in fatty acid oxidation and reductions in hepatic lipid synthesis. LKB1, a serine/threonine protein kinase that also acts as a tumor suppressor, is important in regulating hepatic glucose metabolism by upregulating AMPK.<sup>34</sup> Mice lacking LKB1 have been shown to have reduced AMPK activity in the liver and to exhibit increased gluconeogenesis with consequent development of hyperglycemia that no longer responds to metformin.<sup>31</sup> AMPK plays an important role in energy metabolism, including lipid biosynthesis and metabolic homeostasis, by regulating acetyl-CoA carboxylase<sup>35</sup> and fatty acid oxidation,<sup>36</sup> genes associated with hepatic lipogenesis,<sup>37</sup> glucose uptake into muscle,<sup>38,39</sup> and expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase—enzymes involved in gluconeogenesis.<sup>40</sup> AMPK is stimulated by any metabolic stress that lowers or inhibits adenosine triphosphate production (eg, exercise), by variations in glucose levels, and by specific hormones such as leptin and adiponectin.<sup>41</sup>

In clinical trials, metformin has been shown to decrease glycosylated hemoglobin (HbA1c) levels by 1% to 2%,<sup>42–45</sup> and it may be associated with such benefits as weight neutrality or weight loss, improved endothelial function, improved lipid profiles, decreased cardiovascular events, and lower C-reactive protein levels.<sup>31</sup> The most common side effects associated with metformin are gastrointestinal, including nausea, abdominal discomfort, and diarrhea,<sup>44</sup> which are reversible when the dose is reduced or the drug is discontinued. A rare side effect is lactic acidosis,<sup>46</sup> which tends to occur in the setting of certain predisposing conditions, including hypoxemia, renal insufficiency, liver disease, heart failure, respiratory failure, past history of lactic acidosis, decreased tissue

perfusion or hemodynamic instability, hypoxic states or serious acute illness, and metabolic acidosis. Consequently, use of metformin is contraindicated in patients with these underlying conditions.

### Thiazolidinediones

The thiazolidinediones (TZDs) pioglitazone and rosiglitazone reduce insulin resistance<sup>47,48</sup> and lower glucose levels by binding to peroxisome proliferator-activated receptor (PPAR)- $\gamma$ ,<sup>49</sup> a member of the nuclear receptor superfamily of transcription factors. PPAR- $\gamma$  regulates genes involved in adipocyte differentiation and fatty acid uptake and trapping<sup>50</sup> by *transactivation*, interacting with the retinoid X receptor to form heterodimers. It then binds to the PPAR response elements of target genes.<sup>51</sup> PPAR- $\gamma$  also acts by *transrepression*, interfering with other signal-transduction pathways, which is believed to mediate its anti-inflammatory effects.<sup>52</sup> PPAR- $\gamma$  expression is high in adipose tissue and macrophages and low in liver tissue and pancreatic  $\beta$ -cells. It is also low in muscle tissue—the major player affecting peripheral insulin sensitivity. Despite the low expression of PPAR- $\gamma$  in nonadipose tissues, PPAR- $\gamma$  agonists have been shown to reduce whole-body insulin resistance, even in adipose-specific PPAR- $\gamma$  knockout animal models,<sup>53</sup> although the mechanism by which this is done is unclear.<sup>50</sup> It has been purported that TZD-mediated PPAR- $\gamma$  activation improves insulin sensitivity in a number of ways: (1) by sequestering fat deposition in adipose tissue away from muscle and liver tissue; (2) by increasing levels of adiponectin,<sup>54,55</sup> which has been inversely associated with insulin resistance<sup>24</sup>; and (3) by direct effects on receptors in muscle.<sup>53,56</sup> However, because of the various effects of PPAR- $\gamma$  activation in different tissues, the underlying mechanisms by which TZDs reduce insulin resistance in humans remain unclear and are likely multifaceted.<sup>57</sup>

In clinical trials, treatment with TZDs has been shown to reduce HbA1c levels by 1.0% to 1.5%.<sup>58–62</sup> In addition to this class effect, there appear to be effects specific to each of the drugs in the class. Although both pioglitazone and rosiglitazone have been associated with increased high-density lipoprotein cholesterol (HDL-C) levels, pioglitazone has been associated with reduced low-density lipoprotein cholesterol (LDL-C) and triglyceride levels, whereas rosiglitazone has been associated with an increase in both LDL-C and triglyceride levels.<sup>63,64</sup> Additionally, treatment with pioglitazone has been shown to reduce

macrovascular disease risk,<sup>65,66</sup> whereas recent meta-analyses have suggested an increased risk of cardiovascular disease (CVD) with rosiglitazone.<sup>67,68</sup> As a result of this potential increased CVD risk, the US Food and Drug Administration (FDA) issued a black box warning for rosiglitazone, stating that this drug may cause myocardial ischemia in some patients and therefore is not recommended for use with either insulin or nitrates.<sup>69</sup>

Side effects attributed to TZDs include weight gain of up to 4.2 kg,<sup>59,63</sup> edema,<sup>70,71</sup> heart failure,<sup>72</sup> a decrease in bone density,<sup>73–78</sup> and worsening of preexisting macular edema.<sup>79,80</sup> Therefore, TZDs should not be used in patients with symptomatic congestive heart failure (New York Heart Association [NYHA] class III or IV), and they should be used with caution in patients with osteoporosis and preexisting macular edema.

For many years, metformin and TZDs were the only pharmacologic treatments that targeted insulin resistance. Although these medications are effective both in improving diabetes control and in reducing the risk for diabetes-related complications, a subset of patients with diabetes cannot be treated with these drugs because of possible adverse effects. Given the number of patients with diabetes who also have disorders that would preclude them from using these drugs, alternative pharmacologic options for reducing insulin resistance have been needed.

#### KEY POINT

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### NEW TREATMENTS FOR INSULIN RESISTANCE

Within the past 5 years, new classes of drugs with potential benefits for patients with diabetes and associated insulin resistance have been discovered; these classes include the incretin analogs, dipeptidylpeptidase (DPP)-4

inhibitors, and endocannabinoid inhibitors. Exenatide, an incretin analog, and sitagliptin, a DPP-4 inhibitor, have recently received approval from the FDA for use in the treatment of diabetes. Rimonabant, an endocannabinoid inhibitor, has been approved in Europe for obesity treatment, but it has not yet received approval in the United States.

### KEY POINT

**New classes of drugs with potential benefits for patients with diabetes and associated insulin resistance have been discovered—incretin analogs, DPP-4 inhibitors, and endocannabinoid inhibitors.**

### Incretin Analogs

Incretins are intestinal hormones that are released in response to nutrient ingestion. These hormones stimulate insulin secretion by the  $\beta$ -cells of the pancreatic islets. More than half of the insulin secreted in response to oral ingestion is attributable to the effect of incretin hormones.<sup>81</sup> Two incretins have been identified—glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide (GLP)-1. GIP is secreted from the K cells of the small intestine, whereas GLP-1 is secreted from the L cells of the ileum and colon by both vagal<sup>82</sup> and direct nutrient<sup>83</sup> stimulation. The focus of pharmacologic intervention with incretins has been directed toward GLP-1 rather than GIP because metabolic effects in patients with diabetes have been demonstrated with GLP-1 but not with GIP.<sup>84</sup> In addition to its insulin stimulatory effect,<sup>81</sup> GLP-1 has been shown to promote insulin synthesis, inhibit glucagon secretion,<sup>85,86</sup> increase satiety, and slow gastric emptying via receptors found in the pancreas, hypothalamus, and stomach, among other organs. Moreover, in animal and in vitro studies, GLP-1 appears to inhibit  $\beta$ -cell apoptosis<sup>86–89</sup> and promote  $\beta$ -cell proliferation.<sup>90–92</sup>

Insulin sensitivity has been shown to improve after GLP-1 administration in both in vitro and animal studies,<sup>93–95</sup> as well as human studies.<sup>96–99</sup> Improvement in insulin sensitivity also has been attributed to GLP-1–associated inhibition of glucagon secretion and promo-

### KEY POINT

**GLP-1 has been shown to promote insulin synthesis, inhibit glucagon secretion, increase satiety, and slow gastric emptying. It also appears to inhibit  $\beta$ -cell apoptosis and promote  $\beta$ -cell proliferation.**

tion of weight loss, presumably due to increased satiety and slowed gastric emptying<sup>81,97–99</sup>; however, the mechanism by which GLP-1 and its analogs improve insulin sensitivity is not clear. Results of in vitro and animal studies<sup>93–95</sup> suggest that the effect of GLP-1 on insulin sensitivity may be independent of the associated improvements in glucotoxicity and may involve downstream effects on the insulin-signaling pathway.

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In Vancouver diabetic fatty (VDF) (fa/fa) Zucker (ZDF) rats—an animal model of type 2 DM—treatment with exendin-4, a GLP-1 analog, for 5 weeks improved glycemic control.<sup>95</sup> Results of this study showed a 50% improvement in insulin sensitivity as measured by the glucose infusion rate (GIR) required to maintain stable glucose levels during a hyperinsulinemic-euglycemic clamp. Similar findings were observed in a study of nondiabetic obese fa/fa Zucker rats,<sup>93</sup> which share the same leptin mutation as do the ZDF rats. The nondiabetic rats are hyperphagic and insulin resistant, but they have normal or slightly elevated glucose levels with hyperinsulinemia. In this study, the rats were divided into 3 treatment

groups: a saline BID, fed ad libitum (control) group ( $n = 11$ ); an exenatide BID, fed ad libitum (exenatide) group ( $n = 10$ ); and a saline BID, pair-fed with exenatide (pair-fed) group ( $n = 10$ ). During the 6 weeks of the study, all groups gained weight (237, 166, and 181 g, respectively), but weight gain was significantly lower in the exenatide and pair-fed groups than in the control group ( $P < 0.001$ ). The pair-fed group exhibited a decreased intake of food that was comparable to that of the exenatide group. Both the exenatide and the pair-fed groups had significantly lower HbA1c and insulin levels than did the control group at the end of the treatment period ( $P < 0.05$ ), but glucose levels were not different between groups. During the hyperinsulinemic-euglycemic clamp, the GIR required to maintain euglycemia was significantly higher for the exenatide group than for the control or pair-fed group (53.3 [4.8] vs 21.3 [3.6] and 40.0 [3.8]  $\mu\text{mol/kg}$  per min, respectively;  $P < 0.05$  for both comparisons), indicating greater insulin sensitivity in the exenatide group. This finding was corroborated with an insulin sensitivity index (GIR to insulin concentration), which was higher in the exenatide group than in either the control group or the pair-fed group (224% and 61%, respectively;  $P < 0.003$  for both comparisons). These results showed that exenatide improved insulin sensitivity by a magnitude beyond that which could be explained by weight loss and changes in glycemic parameters alone, suggesting that the effect of exenatide on insulin sensitivity may be through mechanisms that are independent of the associated improvements in glucotoxicity.

Improvement in insulin sensitivity with GLP-1 administration has also been demonstrated in a randomized controlled trial of patients with type 2 DM.<sup>96</sup> Nineteen patients were randomly assigned either to GLP-1 or saline as a continuous subcutaneous infusion via an insulin pump for 6 weeks. Insulin sensitivity measured by hyperinsulinemic-euglycemic clamp at the end of the study period increased by 77% in the GLP-1 group compared with no change in the saline group ( $P = 0.02$ ).

To elucidate the mechanisms by which GLP-1 reduces insulin resistance, *in vitro* and animal studies have been conducted to investigate its effect in muscle and adipose tissue—the main sites of peripheral insulin action. Incubation of mouse skeletal muscle,<sup>100</sup> L6 myotubes,<sup>94</sup> 3T3-L1 adipocytes,<sup>101</sup> and human myocytes<sup>102,103</sup> with GLP-1 was associated with increased glycogen synthase- $\alpha$  activity, glycogen synthesis, and glucose

uptake—measures of insulin sensitivity—which appear to be mediated by activation of PI3K/PKB<sup>94,101,102</sup> and upregulation of IRS-1, IR- $\beta$ , and glucose transporter (GLUT)-4 expression.<sup>101</sup> Similarly, GLP-1 administered in a recombinant adenoviral vector to obese diabetic mice increased insulin sensitivity, as determined by increased glucose transport and uptake in adipocytes, and was associated with increased activation of IRS-1, protein kinase C, and AKT in muscle.<sup>104</sup>

Together, these findings demonstrate the potential role of GLP-1 as a pharmacotherapeutic option for the treatment of diabetes to improve insulin secretion and insulin sensitivity and to promote weight loss. Whereas the development of GLP-1 for the treatment of diabetes has been limited by its short half-life (<2 minutes) due to rapid degradation by the enzyme DPP-4, a number of GLP-1 analogs that demonstrate a longer half-life have been developed, one of which (exenatide) has recently been approved by the FDA.

Exenatide, which is administered by injection, has been approved by the FDA for use in patients with type 2 DM who are being treated with a sulfonylurea, metformin, or a TZD. In clinical trials,<sup>105–110</sup> exenatide lowered HbA1c levels by 0.8% to 1.0% over 30 weeks; it was also associated with a weight loss of 1.5 to 3.0 kg, which was progressive and continued beyond the study duration. Nausea is the most common side effect with the use of exenatide, affecting up to 40% of patients, but it can be minimized by titrating the dose slowly.<sup>105–110</sup> It also tends to subside with continued use. Hypoglycemia is rarely seen, except when administered with an insulin secretagogue or insulin. Exenatide should not be prescribed to patients with gastroparesis or severe chronic kidney disease.

### Dipeptidylpeptidase-4 Inhibitors

DPP-4 inhibitors block DPP-4, an enzyme that degrades endogenous GLP-1. Similar to the GLP-1 analogs, DPP-4 inhibitors have been shown to stimulate insulin secretion and inhibit glucagon secretion<sup>86</sup> and to increase postmeal insulin sensitivity.<sup>111</sup> They do not appear to significantly decrease gastric emptying or promote weight loss.

As with the GLP-1 analogs, DPP-4 inhibitors have been shown to improve insulin sensitivity. Six pairs of VDF (fa/fa) Zucker rats were randomly assigned to receive the DPP-4 inhibitor P32/98 (10 mg/kg) or placebo

**KEY POINT**

**DPP-4 inhibitors, agents that block DPP-4, an enzyme that degrades GLP-1, have been shown to stimulate insulin secretion, inhibit glucagon secretion, and increase postmeal insulin sensitivity, but they do not appear to significantly decrease gastric emptying or promote weight loss.**

BID for 100 days.<sup>112</sup> Insulin sensitivity measured by basal and insulin-stimulated glucose uptake in the soleus muscle at the end of the treatment period was increased by 20% and 50%, respectively, in the animals treated with the DPP-4 inhibitor compared with those in the placebo group. In another study,<sup>111</sup> 57 patients with type 2 DM were randomized to receive the DPP-4 inhibitor vildagliptin (50 mg) or placebo once daily. Insulin sensitivity after meal ingestion (oral glucose insulin sensitivity) improved by 12.5% in the vildagliptin group compared with no change in the placebo group. The mechanism by which DPP-4 inhibition improves insulin sensitivity is presumably mediated by the effects of GLP-1.

In clinical trials of patients with type 2 DM, DPP-4 inhibitors lowered HbA1c levels by a mean of 0.7% over 12 to 52 weeks.<sup>113–126</sup> Most of these studies were conducted using sitagliptin, the only drug in the class currently approved by the FDA, or vildagliptin. Other DPP-4 inhibitors, including saxagliptin and alogliptin, are also in development.

The advantages of the DPP-4 inhibitors over the GLP-1 analogs include their oral administration and the absence of significant side effects, particularly nausea<sup>113</sup>; however, patients do not derive the additional benefit of weight loss associated with GLP-1 analogs. Longer follow-up studies are needed to ensure continued safety with the DPP-4 inhibitors.

**Endocannabinoid Inhibitors**

The endocannabinoid system has been found to play an important role in metabolic homeostasis, mediated mainly through the CB<sub>1</sub> receptor,<sup>127</sup> which is found in

brain and adipose tissue, as well as myocardium, endothelium, and liver tissue.<sup>128</sup> Activation of CB<sub>1</sub> receptors in the brain, specifically in the hypothalamus, increases food intake and appetite<sup>129</sup> and decreases satiety. In adipocytes, CB<sub>1</sub> stimulation upregulates lipoprotein lipase activity, leading to increased fat uptake and storage. Similarly, CB<sub>1</sub> activation leads to increased lipogenesis in the liver.<sup>130</sup> Pharmacologic blockade of CB<sub>1</sub> receptors has been shown to reverse the effects seen with CB<sub>1</sub> activation. In animal models, treatment with a CB<sub>1</sub> antagonist has been shown to reduce food intake, promote weight loss, and increase adiponectin levels,<sup>131–133</sup> and to decrease the development of fatty liver.<sup>134</sup> The potential role of CB<sub>1</sub> blockade in diabetes management may be particularly important given the observed increase in levels of adiponectin.<sup>24</sup>

**KEY POINT**

**Activation of CB<sub>1</sub> receptors in the brain, specifically in the hypothalamus, increases food intake and appetite and decreases satiety. Pharmacologic blockage of these receptors has been shown to reduce food intake, promote weight loss, and increase adiponectin levels.**

The endocannabinoid inhibitor rimonabant has been approved in Europe for the treatment of obesity. Clinical trials of rimonabant in obese subjects with and without diabetes have shown substantial reductions in weight and improvements in metabolic risk factors.<sup>135–138</sup> Overall, overweight and obese patients were able to achieve greater weight loss with rimonabant 20 mg daily for 1 year than with placebo (6–8 vs 1.5–2 kg, respectively), with associated improvements in lipid profiles (specifically, HDL-C and triglyceride levels), adiponectin levels, and incidence of metabolic syndrome.<sup>135–137</sup> However, the changes in lipid and adiponectin levels were thought to exceed those expected with the magnitude of observed weight loss alone and have been attributed to effects independent of the drug.<sup>135</sup> Moreover, small reductions in fasting glucose levels (–0.48 to –0.69 mg/dL according

to method of imputation) and small but significant reductions in insulin levels ( $-2.2$  to  $-2.8$   $\mu\text{IU/mL}$ ;  $P < 0.001$ ) were also observed.<sup>137</sup> In a study investigating the effect of rimonabant versus placebo in overweight and obese patients with type 2 DM,<sup>138</sup> similar reductions in weight and improvements in lipid levels and incidence of metabolic syndrome were observed. Significant reductions in HbA1c ( $-0.6\%$  vs  $0.1\%$ , respectively;  $P < 0.001$ ) and a higher proportion of participants reaching HbA1c levels  $<6.5\%$  ( $43\%$  vs  $21\%$ , respectively;  $P < 0.001$ ) were also observed.

The most common adverse effects with rimonabant are nausea, diarrhea, dizziness, and anxiety, all of which appear to improve after the first few months of treatment.<sup>135–138</sup> Depressed mood was the most common cause of discontinuation in clinical trials.

Taken together, these findings suggest that CB<sub>1</sub> blockade may provide the clinically important benefits of weight reduction and improved cardiovascular and metabolic parameters, particularly for high-risk patients such as those with diabetes.

## CONCLUSIONS

Insulin resistance, a major player in the pathophysiology of type 2 DM, is an important target in the treatment of type 2 DM. For many years, the pharmacologic options for reducing insulin resistance have been limited to metformin and the TZDs; however, promising new treatments have recently emerged. These treatments, including the GLP-1 analogs and DPP-4 inhibitors, which take advantage of the incretin system, and rimonabant, which takes advantage of the endocannabinoid system, not only help improve glycemic control but also offer the potential for additional metabolic and cardiovascular benefits.

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**Address correspondence to:** Mary K. Rhee, MD, Emory University School of Medicine, Department of Medicine, Division of Endocrinology, Metabolism, and Lipids, 49 Jesse Hill Jr Drive, SE, Atlanta, GA 30303. E-mail: mrhee@emory.edu