Patient Tolerance and Acceptance of Colesevelam Hydrochloride: Focus on Type-2 Diabetes Mellitus
Luigi Brunetti, PharmD, MPH, BCPS, CGP; and Evelyn Hermes DeSantis, PharmD, BCPS

ABSTRACT
Diabetes mellitus (DM) is a chronic disease with significant public health implications. The worldwide and U.S. prevalence of DM are 347 million and 25.8 million, respectively.1–2 Type-2 diabetes mellitus (T2DM) represents 90% to 95% of all cases of diabetes.2 In the U.S., DM is a leading cause of blindness, cardiovascular disease, kidney failure, lower limb amputations, and stroke.2 In terms of health care resource burden, direct and indirect medical costs associated with DM were estimated at $176 billion and $69 billion, respectively, in the U.S. in 2012.3 Globally, DM was estimated to be associated with $376 billion in overall expenditures in 2010.4,5

Despite the known morbidities, increased mortality, and increased health care burden associated with T2DM, the majority of patients do not achieve their hemoglobin A1c (HbA1c) goals.6 Nonadherence to oral hypoglycemic agents is common around the world and is a contributing factor to lackluster attainment of treatment goals.7–12 Adverse drug events or poor tolerability may contribute to nonadherence; therefore, strategies to improve tolerability are important. Colesevelam, a second-generation bile acid resin, was designed with greater specificity and affinity for bile acids. Its physiochemical attributes contribute to an improved tolerability profile. Colesevelam has demonstrated efficacy in lowering HbA1c in addition to low-density lipoprotein-cholesterol, although clinical outcomes data are lacking. Several mechanisms of colesevelam’s effect in T2DM have been proposed, including effects on insulin sensitivity and secretion, incretin effects, changes in bile acid composition, and splanchnic sequestration of mealtime glucose. Colesevelam is associated with reductions in HbA1c in T2DM patients ranging from 0.32 to 1.1 percentage points. Colesevelam is generally well tolerated, and indirect comparisons with cholestyramine suggest that it is associated with fewer gastrointestinal symptoms. Reported adherence and persistence to colesevelam treatment in observational studies are 33.3% and 49%, respectively.

INTRODUCTION
Diabetes mellitus (DM) is a chronic disease with significant public health implications. The worldwide and U.S. prevalence of DM are 25.8 million and 90–95% of all cases are type-2 diabetes mellitus (T2DM). Despite the known mortality and morbidity associated with T2DM, the majority of patients do not achieve their hemoglobin A1c (HbA1c) goals. Nonadherence is one of the contributing factors to the lackluster attainment of treatment goals. Drug tolerability may impact medication nonadherence; therefore, strategies to improve tolerability are important. Colesevelam, a second-generation bile acid resin, was designed with greater specificity and affinity for bile acids. Its physiochemical attributes contribute to an improved tolerability profile. Colesevelam has demonstrated efficacy in lowering HbA1c in addition to low-density lipoprotein-cholesterol, although clinical outcomes data are lacking. Several mechanisms of colesevelam’s effect in T2DM have been proposed, including effects on insulin sensitivity and secretion, incretin effects, changes in bile acid composition, and splanchnic sequestration of mealtime glucose. Colesevelam is associated with reductions in HbA1c in T2DM patients ranging from 0.32 to 1.1 percentage points. Colesevelam is generally well tolerated, and indirect comparisons with cholestyramine suggest that it is associated with fewer gastrointestinal symptoms. Reported adherence and persistence to colesevelam treatment in observational studies are 33.3% and 49%, respectively.

CLINICAL EFFICACY
Detailed summaries of the clinical efficacy of colesevelam for the treatment of T2DM have been published previously.34,35 Colesevelam produces significant reductions in fasting plasma glucose, HbA1c, and LDL-C.27 Reductions in HbA1c from baseline based on data from clinical studies evaluating colesevelam monotherapy for hypercholesterolemia,34,35 Although colesevelam has demonstrated efficacy in reducing plasma glucose, its mechanism for this action is uncertain. Several authors have provided detailed overviews of the current understanding of the mechanism of action for lowering glucose.24–27 Numerous mechanisms have been proposed, including effects on insulin sensitivity and secretion, incretin effects, changes in bile acid composition, and splanchnic sequestration of mealtime glucose.24,26,28–32 However, more recently, the effects of colesevelam on insulin sensitivity and secretion have been refuted.36 Current evidence suggests that intestinal TGR5 activation secondary to bile acid binding yields increased concentrations of glucagon-like peptide-1 (GLP-1) or other incretins and inhibition of glycogenolysis.36 Figure 1 illustrates the various mechanisms thought to result in colesevelam’s glucose-lowering effects.27 Overall, the mechanism is elusive and many questions remain to be answered. One conclusion that can be reached is that the mechanism is unique and different from other oral hypoglycemic agents.26,33 The ability to lower LDL-C and glucose with a novel mechanism makes colesevelam an attractive option.

Historically, the use of first-generation bile acid resins (i.e., cholestyramine and colestipol) has been associated with poor tolerability because of a gritty taste and constipation, hence their limited use.16,17 Colesevelam (WelChol, Daiichi Sankyo), a second-generation bile acid resin, has been reported to be better tolerated compared with other bile acid resins.18 As such, adherence should be improved with this agent. This article provides clinicians with an overview of the safety and tolerability of colesevelam with a focus on T2DM.

MECHANISM OF ACTION
Like other bile acid resins, colesevelam decreases low-density lipoprotein-cholesterol (LDL-C). Previous research has provided evidence on the mechanism of action for cholesterol reduction and has been discussed in detail elsewhere.19–23 Expected reductions in LDL-C range from 10% to 20% from baseline based on data from clinical studies evaluating colesevelam monotherapy for hypercholesterolemia.34,35

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Detailed summaries of the clinical efficacy of colesevelam for the treatment of T2DM have been published previously.34,35 Colesevelam produces significant reductions in fasting plasma glucose, HbA1c, and LDL-C.27 Reductions in HbA1c from baseline in patients with T2DM on concomitant oral hypoglycemic treatment in randomized controlled trials range from 0.32 to 1.1 percentage points.26–38 In comparison with other oral hypoglycemic agents, colesevelam produces smaller reductions in HbA1c.40 In patients with prediabetes (defined as a two-hour post-oral glucose tolerance test glucose level of 140

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Disclosures: The authors report that they have no commercial or financial relationships in regard to this article.
to 199 mg/dL, fasting plasma glucose of 110 to 125 mg/dL, or both), reductions in HbA1c have been modest (a 0.12 percentage point reduction from baseline).

LDL-C reductions of approximately 13% to 17% from baseline were reported in T2DM randomized controlled trials, similar to reductions seen in the hypercholesterolemia population.

HbA1c reductions seen in clinical trials have been validated in a real-world population using a large electronic medical record database (GE Centricity). The observed HbA1c percentage-point reductions ranged from 0.47 (at 16-week follow-up) to 0.44 (at 26-week follow-up). The reductions were maintained at 52 weeks with a mean HbA1c reduction of 0.46 percentage points.

**SAFETY AND TOLERABILITY**

Early-generation bile acid resins have been approved by the Food and Drug Administration (FDA) since the early 1970s for the treatment of hyperlipidemia. Colesevelam gained approval for the treatment of adult patients with T2DM in combination with a sulfonylurea, metformin, and/or insulin in 2008. Adverse effects are relatively benign, with most being gastrointestinal (GI) in nature. GI side effects are important because these symptoms have been associated with reduced health-related quality of life in patients with T2DM treated with oral hypoglycemic agents.

The most common adverse events reported with colesevelam in randomized controlled trials evaluating its use in T2DM are summarized in Table 1. As expected, flatulence, constipation, and dyspepsia were the most common adverse drug events, occurring in approximately 18%, 18%, and 10% of patients, respectively.

GI side effects are also common with oral hypoglycemic agents, particularly metformin and alpha-glucosidase inhibitors. The incidence of GI adverse effects, including nausea, diarrhea, flatulence, and abdominal pain, with metformin is approximately 30%; however, these effects are transient and can often be minimized by slow titration and administration with meals. Discontinuation of metformin due to adverse drug events is uncommon (3%). Similarly, discontinuation rates with colesevelam in clinical trials have been low (Table 2).

The safety and tolerability of colesevelam were confirmed in a long-term extension study. Patients completing one of the three phase 3 randomized controlled trials were allowed to enroll in a 52-week open-label extension study. Of the 361 subjects who entered the extension study, 70.9% experienced an adverse event, the majority (88.1%) of which were mild or moderate in nature. However, only 11% were considered drug-related adverse events. GI complaints were common among drug-related adverse events. Discontinuation due to drug-related adverse events was uncommon, occurring in only 3.1% of subjects. Collectively, data from randomized controlled trials and the extension study support the safety and tolerability of colesevelam for the treatment of T2DM.

### Table 1 Adverse Events Reported in Clinical Trials

<table>
<thead>
<tr>
<th>Event</th>
<th>Colesevelam (N = 535)</th>
<th>Placebo (N = 528)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>322 (60.2)</td>
<td>289 (54.7)</td>
</tr>
<tr>
<td>Drug-related adverse events</td>
<td>100 (18.7)</td>
<td>48 (9.1)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>27 (5.0)</td>
<td>24 (4.5)</td>
</tr>
</tbody>
</table>

Most common drug-related adverse events occurring in ≥ 2% of patients:

- Constipation: 35 (35)
- Dyspepsia: 15 (15)
- Diarrhea: 5 (5)
- Flatulence: 7 (7)
- Hypoglycemia: 10 (10)

<table>
<thead>
<tr>
<th>Event</th>
<th>Colesevelam (N = 535)</th>
<th>Placebo (N = 528)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation: 35 (35)</td>
<td>8 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia: 15 (15)</td>
<td>6 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea: 5 (5)</td>
<td>5 (10.4)</td>
<td></td>
</tr>
<tr>
<td>Flatulence: 7 (7)</td>
<td>4 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia: 10 (10)</td>
<td>10 (20.8)</td>
<td></td>
</tr>
</tbody>
</table>

*Percentage of drug-related adverse events

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TOLERABILITY COMPARED WITH THAT OF EARLIER-GENERATION BILE ACID RESINS

Although earlier-generation bile acid resins are safe, patients taking them did not tolerate therapy well. Colesevelam was engineered with greater specificity and affinity for bile acids compared with earlier-generation bile acid resins.18,45 These attributes result in a greater potency on a weight-by-weight basis versus early-generation bile acid resins; therefore, smaller amounts of colesevelam can be used to achieve similar therapeutic efficacy while minimizing adverse effects.46 Furthermore, packaging colesevelam as tablets rather than a slurry (as with cholestyramine) may make the agent more tolerable.35

Discontinuation rates for early-generation bile acid resins have been reported to range from 34% to 60%.17,48,49 The reasons for frequent discontinuation with these agents are multifactorial and include high frequency of GI side effects, complicated dosing schedules, and poor palatability of the slurry.17,48,49 Constipation occurs frequently in cholestyramine-treated patients (28% to 39%), as do gas, bloating, flatulence, and cramping (12% of patients).18 Few studies have evaluated early-generation bile acid sequestrants in the DM population, making comparisons to colesevelam difficult.50–52 Further, the majority of these studies enrolled few patients and were relatively short in duration.

Colesevelam has been evaluated in several clinical trials. Overall discontinuation rates in patients with diabetes or prediabetes treated with colesevelam ranged from 11% to 28% (Table 2).36–39,41,53–57 Furthermore, discontinuation rates deemed to be related to colesevelam therapy were lower (0% to 6.5%). Very few data have directly compared the tolerability of colesevelam with early-generation bile acid resins. Two nonrandomized studies compared colesevelam to earlier-generation bile acid resins. In a survey of 10 patients with Crohn’s disease previously taking cholestyramine who were switched to colesevelam, nine reported that colesevelam was...

### Table 2 Patient Discontinuation in Clinical Trials of Colesevelam in Type-2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Any DC</th>
<th>DC Due to Any AE</th>
<th>DC Due to Drug-Related AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenstock, 2012</td>
<td>Post hoc analysis of data from a 16-week, randomized, double-blind, placebo-controlled study, N = 179</td>
<td>Drug-naïve Hispanic patients with diabetes, add-on to metformin or metformin alone</td>
<td>Not reported</td>
<td>C, 3% P, 8%</td>
<td>C, 3% P, 6%</td>
</tr>
<tr>
<td>Goldberg, 2013</td>
<td>16-week, randomized, double-blind, placebo-controlled, N = 216</td>
<td>Prediabetes and primary hyperlipidemia</td>
<td>C, 11% P, 14.8%</td>
<td>C, 0% P, 0%</td>
<td>C, 0% P, 0%</td>
</tr>
<tr>
<td>Rosenstock, 2012</td>
<td>Post hoc analysis of data from a 16-week, randomized, double-blind, placebo-controlled study, N = 153</td>
<td>Hispanic patients with primary hyperlipidemia and prediabetes, monotherapy</td>
<td>Not reported</td>
<td>C, 1% P, 3%</td>
<td>C, 1% P, 3%</td>
</tr>
<tr>
<td>Handelsman, 2010</td>
<td>16-week, randomized, double-blind, placebo-controlled, N = 216</td>
<td>Untreated prediabetes, monotherapy</td>
<td>C, 11% P, 14.8%</td>
<td>C, 1.9% P, 1.9%</td>
<td>C, 1.9% P, 1.9%</td>
</tr>
<tr>
<td>Rosenstock, 2010</td>
<td>16-week, randomized, double-blind, placebo-controlled, N = 286</td>
<td>Diabetes and hypercholesterolemia, add-on to metformin versus metformin alone</td>
<td>C, 14.5% P, 14.9%</td>
<td>C, 4.1% P, 5.7%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rigby, 2010</td>
<td>16-week, open-label, randomized pilot study, N = 169</td>
<td>Diabetes, add-on to metformin versus rosiglitazone or sitagliptin add-on</td>
<td>Not reported</td>
<td>C, 5.3% R, 1% S, 1%</td>
<td>C, 5.3% R, 1% S, 1%</td>
</tr>
<tr>
<td>Bays, 2008</td>
<td>24-week, randomized, double-blind, placebo-controlled, N = 216</td>
<td>Diabetes, add-on to metformin</td>
<td>C, 27% P, 32.4%</td>
<td>C, 5% P, 2.5%</td>
<td>C, 3.8% P, 1.3%</td>
</tr>
<tr>
<td>Fonseca, 2008</td>
<td>26-week, randomized, double-blind, placebo-controlled, N = 461</td>
<td>Diabetes, add-on to sulfonylureas</td>
<td>C, 27.8% P, 39%</td>
<td>C, 7.8% P, 3.9%</td>
<td>C, 5.2% P, 1.7%</td>
</tr>
<tr>
<td>Goldberg, 2008</td>
<td>16-week, randomized, double-blind, placebo-controlled, N = 287</td>
<td>Diabetes, add-on to insulin</td>
<td>C, 20.7% P, 18.6%</td>
<td>C, 6.8% P, 2.1%</td>
<td>C, 3.4% P, 1.4%</td>
</tr>
<tr>
<td>Zieve, 2007</td>
<td>12-week, randomized, double-blind, placebo-controlled, N = 65</td>
<td>Diabetes, inadequately controlled with current medications</td>
<td>C, 12.9% P, 5.9%</td>
<td>C, 6.5% P, 2.9%</td>
<td>C, 6.5% P, 2.9%</td>
</tr>
</tbody>
</table>

AE = adverse event; C = colesevelam; DC = discontinuation; P = placebo; R = rosiglitazone; S = sitagliptin
ADHERENCE AND PERSISTENCE TO THERAPY

Given the pharmacological characteristics of colesevelam, it is expected that adherence to therapy and in turn patient outcomes would be improved. In a retrospective cohort study using a large administrative claims data set, patients who were adherent to colesevelam were 43% less likely to experience an acute myocardial infarction or stroke hospitalization (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.44–0.73; P < 0.0001). In this analysis of more than 42,000 adults, only 33.3% were adherent or partially adherent (defined as a proportion of days covered by prescription claims during the one-year follow-up period of 0.8 or more and 0.5 to 0.8, respectively). This reported percentage is in stark contrast to adherence rates observed in a randomized controlled trial in which 88% of patients were adherent. Adherence with cholestyramine was reported as 43% in a randomized study designed to determine the adherence and efficacy of pravastatin and cholestyramine (monotherapy or in combination). Although this number is slightly better than that of the observational study with colesevelam, one must interpret this finding with caution. First, adherence in controlled clinical studies is often inflated owing to formal evaluation of adherence, availability of personnel to address patient concerns and to support adherence by offering patients advice, and screening out nonadherent patients prior to enrollment. In fact, adherence rates with cholestyramine in observational studies were poor, with one large prescription claims analysis reporting that patients treated with cholestyramine did not have enough of the drug to cover 63% of days. Second, the populations in the studies are heterogeneous, making direct comparisons challenging. Third, adherence rates in the T2DM population may differ from those seen in patients with hypercholesterolemia.

Persistence to colesevelam treatment among patients with hypercholesterolemia, defined as no medication order gap of more than 30 days during a 12-month period, was reported as 49% in a cohort study. The authors performed a multivariate analysis and identified an inverse relationship between female gender and odds of colesevelam persistence. Concomitant intestinal cholesterol absorption inhibitor use and baseline LDL-C at goal were associated with greater odds of persistence. No data on persistence specific to T2DM are currently available. One-year persistence of initial therapy with metformin, sulfonylureas, or metformin/sulfonylurea combinations was reported as 47.7%, 45.4%, and 55.8%, respectively. However, the deduction that persistence rates with colesevelam are comparable to oral hypoglycemic agents ultimately requires direct comparisons in the target population (T2DM).

STRAIGHT TO IMPROVE PATIENT SAFETY, TOLERABILITY, AND ADHERENCE

Despite the availability of several options for treating T2DM, many patients have comorbidities that limit the viable treatment options. Comorbidities, present in up to 60% of individuals with T2DM, often increase the risk of toxicity and distort the risk–benefit ratio. Current American Diabetes Association guidelines recommend individualizing patient therapy. To apply this concept, clinicians must be familiar with common adverse drug events and tolerability concerns with the various treatments.

Although colesevelam was well tolerated in clinical trials among a wide variety of demographics, it is not without risk of important adverse effects. Colesevelam, like other bile acid resins, has the potential to cause constipation and should be avoided in patients with GI motility disorders. In patients facing planned GI surgeries, the use of colesevelam may increase the risk of bowel obstruction; therefore, alternative strategies for treatment of T2DM should be considered immediately after surgery to allow the GI system to recover. Similarly, in patients with compromised GI transit (i.e., gastroparesis), the use of colesevelam should be avoided. The advantages and disadvantages of colesevelam are summarized in Table 3.

### Table 3 Advantages and Disadvantages of Colesevelam

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Novel mechanism for glucose lowering</td>
<td>• May elevate triglycerides</td>
</tr>
<tr>
<td>• Lowers low-density lipoprotein-cholesterol</td>
<td>• Avoid use in patients with bowel obstruction</td>
</tr>
<tr>
<td>• Lowers hemoglobin A1c (HbA1c)</td>
<td>• Caution when using in patients with dysphagia</td>
</tr>
<tr>
<td>• Available as tablets and powder for reconstitution</td>
<td>• Limited outcomes data</td>
</tr>
<tr>
<td>• Weight-neutral</td>
<td>• Few direct comparisons to early-generation bile acid sequestrants</td>
</tr>
<tr>
<td>• No systemic drug interactions</td>
<td>• Cost</td>
</tr>
<tr>
<td>• Safe in renal disease</td>
<td>• Gastrointestinal side effects</td>
</tr>
<tr>
<td>• Safe in hepatic disease</td>
<td>• May decrease absorption of other medications</td>
</tr>
<tr>
<td>• No hypoglycemia</td>
<td>• Modest HbA1c reductions</td>
</tr>
<tr>
<td>• Pregnancy category B</td>
<td>• May decrease absorption of fat-soluble vitamins. Patients should take vitamins four hours before colesevelam</td>
</tr>
</tbody>
</table>

Triglycerides are increased with all bile acid resins in a dose-dependent fashion. The increase is related to activation of phosphatidic acid phosphatase and triggering of alpha-glycerol phosphate conversion to triglycerides and phospholipids in the liver. Colesevelam should not be used in patients with triglyceride levels greater than 500 mg/dL due to the risk of pancreatitis. Additionally, clinicians should be aware that patients with triglyceride levels greater than 300 mg/dL were excluded from clinical trials; therefore, experience in this
population is limited. Hypertglycemia and pancreatitis are common in patients with T2DM; therefore, consideration of this limitation is clinically relevant.

Drug interactions are often associated with fluctuations in systemic drug concentrations. These fluctuations may result in suboptimal or exaggerated responses. While pharmacokinetic interactions are unlikely with colesevelam because it is not systemically absorbed, colesevelam may bind drugs in the gut, resulting in decreased absorption of the subject drug. The cross-linked epchlorohydrin structure of colesevelam decreases the potential for interactions in the GI tract lining.

Although binding of drugs in the GI tract should be less common with colesevelam than with early-generation bile acid resins, it is prudent to stagger the administration of colesevelam with other medications. Many medications have not been formally evaluated for their binding potential with colesevelam.

The choice of drug formulation to prescribe is dependent on the patient. For example, in patients with difficulty swallowing colesevelam tablets, the powder for reconstitution may be used. Various fluids may be used to reconstitute colesevelam powder. Allowing the patient to choose water, carbonated beverages, fruit juices, or milk as the fluid used for reconstitution may improve patient tolerability.

Acknowledging and managing the aforementioned concerns may alleviate patient apprehensions with colesevelam treatment. Choosing the appropriate patient, dose formulation, and treatment regimen ultimately facilitates patient adherence to therapy.

CONCLUSION

Colesevelam is a second-generation bile acid sequestrant that is safe and effective for reducing HbA1c in patients with T2DM. The current (2013) American Association of Clinical Endocrinologists glycemic control algorithm considers colesevelam an appropriate adjunctive therapy with metformin for patients with a HbA1c of 7.5% or more. Robust comparisons to earlier-generation bile acid sequestrants are lacking; however, colesevelam appears to be better tolerated.

REFERENCES


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