Diabetes mellitus (DM) was the third most common medical diagnosis in 2016. Uncontrolled DM can lead to cardiovascular disease, nephropathy, neuropathy, and retinopathy. It is estimated that only 52.5% of patients with DM have achieved their goal hemoglobin A1c (HbA1c) level. The 2018 American Diabetes Association (ADA) clinical guidelines lack strong recommendations on sequential therapy for patients who have received a diagnosis of type 2 diabetes mellitus (T2DM) and have been unable to achieve their goal HbA1c level with lifestyle changes and maximum-dose metformin. Although those guidelines support treatment intensification with a glucagon-like peptide 1 receptor agonist (GLP-1 RA), prescribing patterns for T2DM most commonly include adding insulin to try to control blood glucose and reduce long-term comorbidities. 

Insulin therapy is known for its ability to effectively lower blood glucose and HbA1c levels but comes with many limitations. Mealtime insulin has the highest risk of hypoglycemia, causes significant weight gain, requires several additional injections per day, and additional monitoring of blood glucose. The 2018 ADA guidelines state that hypoglycemia is the major limiting factor in the management of insulin-treated T2DM.

Compared with mealtime insulin, GLP-1 RAs have the benefit of reducing the risk of hypoglycemia, weight gain, and number of daily injections. In addition, compared with insulin alone, GLP-1 RAs have the advantage of reducing glycemic variability. These advantages are especially attractive in the treatment of geriatric patients. Given its mechanism of action, liraglutide is expected to have an effect on both fasting and postprandial blood glucose. There are no recommendations on how to empirically reduce the dose of insulin when starting liraglutide.

BACKGROUND

GLP-1 is an incretin hormone that is secreted in response to meal ingestion. GLP-1 stimulates insulin release, suppresses elevated glucagon levels, and delays gastric emptying. Patients with a DM diagnosis have impaired secretion of GLP-1.

In July 2016, results of the LEADER trial showed that liraglutide therapy had a cardiovascular benefit in high-risk patients. In October 2017, liraglutide was FDA approved for reducing 3-point major adverse cardiac events.
Xultophy (Novo Nordisk, Plainsboro, NJ) is a fixed-dose medication combining degludec, a long-acting basal insulin analog, with liraglutide. As seen in the DUAL trials, Xultophy was more beneficial in reducing HbA1c levels than each component alone, and minimized hypoglycemic events, weight gain, and complexity of insulin treatment intensification.9-11 Therapy that combines basal insulin and a GLP-1 RA may be more effective than either agent as monotherapy and may have a significant impact on cardiovascular risk because of the synergistic vasodilatory, anti-inflammatory, and antioxidant properties of insulin and GLP-1 RA.6 In addition, combination therapy offers many benefits over traditional basal and bolus insulin regimens. These benefits include fewer daily injections, additional weight reduction resulting from the reduced insulin requirement, and fewer episodes of hypoglycemia. Reported gastrointestinal adverse effects have been transient and were not augmented when a GLP-1 RA was used in combination with basal insulin.11

**METHODS**

We performed a retrospective chart analysis to quantify the benefit of using liraglutide as an add-on therapy to basal and bolus insulin regimens in veterans treated at VA Boston Healthcare System (VABHS). The analysis evaluated changes in insulin doses and HbA1c levels when liraglutide was added to these regimens. Patients identified for the study had electronic medication orders for concurrent therapy with liraglutide, insulin glargine, and insulin aspart filled through outpatient VABHS campus pharmacies for at least 3 months between January 2010 and December 2016. Sixty-nine patients who were on basal-bolus insulin for T2DM and who were prescribed liraglutide for treatment intensification were screened for inclusion and exclusion criteria. Data were analyzed at baseline and 3 months after liraglutide treatment.

**Study Protocol**

The inclusion criteria were patients aged ≥ 18 years, T2DM diagnosis, and therapy with insulin glargine and insulin aspart for at least 3 months before treatment intensification with liraglutide. Exclusion criteria were diagnosis of type 1 DM. To accurately quantify mean change in number of insulin units used, the study included patients only if they had been prescribed insulin glargine and insulin aspart before starting liraglutide. All other insulin regimens were excluded. To detect the true change that occurs when liraglutide is added to basal-bolus insulin, the study also excluded patients if they had been previously prescribed another GLP-1 RA. Patients with contraindications to liraglutide, insulin aspart, or insulin glargine were excluded as well. In addition, patients were excluded from the exposed arm if they were injecting < 1.2 mg of liraglutide once daily or if

---

**TABLE 1 Patients’ Characteristics at Baseline (N = 35)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35 (97.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.5 (9.3)</td>
</tr>
<tr>
<td>Body weight, lb</td>
<td>255.0 (52.2)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>37.4 (6.1)</td>
</tr>
<tr>
<td>Hemoglobin A1c level, %</td>
<td>9.0 (2)a</td>
</tr>
</tbody>
</table>

*aNonnormal distribution median ± interquartile range.*
they had been on liraglutide for < 3 months.

**Study Outcomes**
All 35 patients who met the inclusion and exclusion criteria were included in this retrospective chart review. The primary outcome was determined by changes in HbA1c level and number of insulin doses 3 months after treatment with liraglutide. For each patient, a chart review was performed to determine the amount of insulin added or reduced during the study period. Data were collected at baseline and 3 months after initiation of liraglutide.

**Statistical Analysis**
Statistical analyses were performed with SPSS Version 20.0 (IBM, Armonk, NY). Population characteristics and study outcomes with normal distribution were compared using a paired t test and are reported as means with standard deviations. Nonnormally distributed variables (bolus insulin, HbA1c level) were compared using the nonparametric Wilcoxon rank sum test and are reported as median values with interquartile ranges. Normality was tested with the Shapiro-Wilk test. The primary outcome evaluated was change in number of insulin units used. Secondary outcomes included change in HbA1c level and change in body weight. A Bonferroni correction for multiple comparisons was used to prevent type I error. Significance at the Bonferroni-corrected level of .01 (.05/5 = .01) is indicated.

**RESULTS**
Patients were included if they were previously on insulin glargine and insulin aspart before starting liraglutide for treatment intensification. Although 69 patients matched the initial search, only 35 were included in the analysis owing to insufficient duration of liraglutide therapy (Figure 1). Those patients were not on liraglutide therapy for at least 3 months with HbA1c results to allow for an appropriate analysis.

As Table 1 indicates, 100% of patients were male, and mean (SD) age was 65.5 (9.3) years. Mean (SD) body weight was 255.0 (52.5) lb, mean (SD) body mass index was 37.4 (6.1), and mean (SD) HbA1c level was 9.0% (2.0).
After 3 months of therapy with liraglutide, HbA1c levels were reduced by a mean of 1.0% (P = .005) (Table 2). Results showed a trend, but it was a nonsignificant reduction in amount of insulin required. Mean reduction in basal insulin dose was 11%, and mean reduction in bolus insulin was 33% (Figures 2 and 3). Interestingly, the majority of liraglutide prescriptions were initiated by nonphysicians (74%), either nurse practitioners or pharmacists.

DISCUSSION
After 3 months of treatment with liraglutide, patients experienced a significant decrease in HbA1c levels. Insulin doses also decreased, but this finding was not statistically significant after correcting for multiple testing. These results are similar with those in larger studies of the effectiveness of liraglutide and the addition of liraglutide to insulin therapy. 6,8,12,13 Liraglutide has been shown to decrease HbA1c levels, lower rates of progression of kidney failure, decrease weight, and provide cardiovascular benefit.

In a prospective, randomized controlled trial evaluating the effect of adding liraglutide to insulin therapy, 21 of the 37 patients who had T2DM and required more than 100 total units of basal-bolus insulin daily were initiated on liraglutide, and changes in HbA1c level, body weight, and glycemic variability were compared. Results showed statistically significant improvement in all 3 outcomes in the group treated with liraglutide. 6 Our findings, in conjunction with those of the larger studies, suggest that many of these results are generalizable to our local veteran population. Importantly, liraglutide was successfully started in pharmacy clinics—an indication that this treatment need not be initiated by an endocrine specialist.

Limitations
Given the lack of gender and racial diversity in this study population, our findings have limited generalizability to other populations. It is possible that, with a larger sample size, these results regarding reduced basal insulin doses would be significant. It has been hypothesized that patients experience fewer episodes of hypoglycemia when insulin doses are reduced, but we were unable to measure the frequency of these episodes. Other study limitations include inability to assess adherence and inability to account for concurrent regimens and/or for lifestyle changes that may have been made during the study period. Further, the study did not collect data on changes made to current DM medication regimens during the study period, and these changes may have influenced outcomes.

CONCLUSION
Patients who require treatment intensification for insulin-dependent T2DM may benefit from having liraglutide added to their basal-bolus insulin regimen. Liraglutide may prove to be more favorable than bolus insulin when choosing add-on therapy to basal insulin. Benefits include reductions in insulin doses, HbA1c levels, number of daily injections, and body weight. Therefore, we suggest that empirically reducing basal insulin by 10% to 25% and bolus insulin by 25% to 50% will avoid relative hypoglycemia. Prescribers must keep in mind patient-specific factors when adjusting insulin doses, if these doses are adjusted at all. Follow-up of 2 to 4 weeks is recommended for review of home monitoring of glucose for further insulin adjustments.

This study has important clinical implications. First, the finding of a reduction in HbA1c levels supports use of liraglutide therapy for HbA1c reduction in veterans. Second, the number of veterans who were successfully initiated on liraglutide therapy by nonphysician providers indicates that liraglutide can be effectively and safely

### TABLE 2 Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Baseline (SD)</th>
<th>3 Months (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily basal insulin dose, units</td>
<td>83 (36)</td>
<td>74 (37)</td>
<td>.04</td>
</tr>
<tr>
<td>Daily bolus insulin dose, units</td>
<td>33 (45)</td>
<td>22 (45)</td>
<td>.1</td>
</tr>
<tr>
<td>Hemoglobin A1c level, %</td>
<td>9.0 (2)</td>
<td>8.0 (3)</td>
<td>.005</td>
</tr>
<tr>
<td>Body weight, lb</td>
<td>255.0 (62.2)</td>
<td>259 (48)</td>
<td>.7</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min/1.73 m²</td>
<td>56.5 (17)</td>
<td>59.5 (15)</td>
<td>.7</td>
</tr>
</tbody>
</table>

Median ± interquartile range, compared via Wilcoxon rank sum test (aka Mann-Whitney test).

Significant after correcting for multiple testing.

After 3 months of therapy with liraglutide, HbA1c levels were reduced by a mean of 1.0% (P = .005) (Table 2). Results showed a trend, but it was a nonsignificant reduction in amount of insulin required. Mean reduction in basal insulin dose was 11%, and mean reduction in bolus insulin was 33% (Figures 2 and 3). Interestingly, the majority of liraglutide prescriptions were initiated by nonphysicians (74%), either nurse practitioners or pharmacists.

DISCUSSION
After 3 months of treatment with liraglutide, patients experienced a significant decrease in HbA1c levels. Insulin doses also decreased, but this finding was not statistically significant after correcting for multiple testing. These results are similar with those in larger studies of the effectiveness of liraglutide and the addition of liraglutide to insulin therapy. 6,8,12,13 Liraglutide has been shown to decrease HbA1c levels, lower rates of progression of kidney failure, decrease weight, and provide cardiovascular benefit.

In a prospective, randomized controlled trial evaluating the effect of adding liraglutide to insulin therapy, 21 of the 37 patients who had T2DM and required more than 100 total units of basal-bolus insulin daily were initiated on liraglutide, and changes in HbA1c level, body weight, and glycemic variability were compared. Results showed statistically significant improvement in all 3 outcomes in the group treated with liraglutide. 6 Our findings, in conjunction with those of the larger studies, suggest that many of these results are generalizable to our local veteran population. Importantly, liraglutide was successfully started in pharmacy clinics—an indication that this treatment need not be initiated by an endocrine specialist.

Limitations
Given the lack of gender and racial diversity in this study population, our findings have limited generalizability to other populations. It is possible that, with a larger sample size, these results regarding reduced basal insulin doses would be significant. It has been hypothesized that patients experience fewer episodes of hypoglycemia when insulin doses are reduced, but we were unable to measure the frequency of these episodes. Other study limitations include inability to assess adherence and inability to account for concurrent regimens and/or for lifestyle changes that may have been made during the study period. Further, the study did not collect data on changes made to current DM medication regimens during the study period, and these changes may have influenced outcomes.

CONCLUSION
Patients who require treatment intensification for insulin-dependent T2DM may benefit from having liraglutide added to their basal-bolus insulin regimen. Liraglutide may prove to be more favorable than bolus insulin when choosing add-on therapy to basal insulin. Benefits include reductions in insulin doses, HbA1c levels, number of daily injections, and body weight. Therefore, we suggest that empirically reducing basal insulin by 10% to 25% and bolus insulin by 25% to 50% will avoid relative hypoglycemia. Prescribers must keep in mind patient-specific factors when adjusting insulin doses, if these doses are adjusted at all. Follow-up of 2 to 4 weeks is recommended for review of home monitoring of glucose for further insulin adjustments.

This study has important clinical implications. First, the finding of a reduction in HbA1c levels supports use of liraglutide therapy for HbA1c reduction in veterans. Second, the number of veterans who were successfully initiated on liraglutide therapy by nonphysician providers indicates that liraglutide can be effectively and safely
started in primary care pharmacy clinics, increasing access to the medication.

**Author Affiliations**

Katherine Czarnowski is a Clinical Pharmacist, Bryan Wood is a Pharmacy Residency Director and Clinical Pharmacy Specialist, Patricia Underwood is a Nurse Practitioner in Endocrinology, and Dhiren Patel is a Clinical Pharmacy Specialist, all at VA Boston Healthcare System in Massachusetts. Chirlie Silver is an Adjunct Faculty of Pharmacy Practice at Massachusetts College of Pharmacy and Health Sciences University in Worcester. Dhiren Patel is an Associate Professor of Pharmacy Practice at Massachusetts College of Pharmacy and Health Sciences University in Boston.

**Author disclosures**

Dhiren Patel is on the speaker’s bureaus of AstraZeneca, Boehringer Engelheim, Merck, Novo Nordisk, and Valeritas. He also is on the Advisory Board/Consultant for AstraZeneca, Becton Dickinson, Eli Lilly, Merck, and Sanofi. The other authors report no actual or potential conflicts of interest with regard to this article.

**Disclaimer**

The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, Frontline Medical Communications Inc., the US Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review the complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

**References**


