Hypogonadism in males is a syndrome characterized by low serum testosterone concentrations and accompanying clinical manifestations. Symptoms of low testosterone concentrations include sexual, cognitive, and physical impairment, and may involve a loss of libido, erectile dysfunction, depressed mood and energy, decreases in muscle mass, and declines in bone mineral density. The prevalence of male hypogonadism is estimated to be up to 12% in the general population. The prevalence increases with age, with 50% of men aged 80-90 years experiencing testosterone concentrations below normal.

Attributing hypogonadism to age-related causes requires a differential evaluation for other contributing or causative factors. Factors other than age that increase the likelihood of hypogonadism include comorbid conditions such as type 2 diabetes and cardiovascular disease, as well as chronic opioid use. In addition, there are multiple underlying causes for decreased testosterone concentrations, which include cranial trauma, radiation, chemotherapy, drug-induced abnormalities, chronic infections (HIV), and developmental predispositions such as Klinefelter syndrome. If a contributing comorbid condition is identified, it should ideally be corrected, if possible, rather than starting treatment to reverse low testosterone concentrations.

Hypogonadism falls into three categories: primary, secondary, and mixed. Primary hypogonadism is due to a testicular failure and is characterized by low testosterone and high leutinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations. Conversely, secondary hypogonadism is caused by defects at the hypothalamus or pituitary and is characterized by not only low testosterone, but also low LH and FSH. Age-related declines are often a combination of both primary and secondary, which is important clinically because restoration with testosterone hormone therapy is possible in secondary hypogonadism, but it is not possible in a majority of patients suffering only from primary hypogonadism. Therefore, the initial approach for treating age-related hypogonadism often focuses on exogenous administration of hormones.

Testosterone replacement therapy (TRT) plays a large role in the treatment of male hypogonadism and it is the most commonly used form of therapy. Yet, with the large number of TRT formulations that are currently marketed, choosing an appropriate TRT product is challenging. The goal of this review is to summarize drug therapies used in the setting of male hypogonadism and provide a stepwise approach for medication management.

The decision to begin TRT is dependent on both serum concentrations of testosterone and the presence of symptoms. The Box lists commonly reported symptoms hypogonadism in men. After performing a history and identifying these symptoms, a total testosterone (TT) concentration can be measured as an initial diagnostic test, which is available in most hospital settings. TT is a composite of albumin-bound, free, and sex-hormone binding globulin (SHBG) bound testosterone. Only a small percentage of testosterone circulates freely in the blood, approximately 1-2%. The remaining testosterone binds to either SHBG (50-60%)...
or albumin (40-50%). Because of an inherently strong interaction between testosterone and SHBG, only the free and albumin-bound testosterone are considered biologically available. Additionally, SHBG concentrations can be altered depending on different factors such as obesity, hypothyroidism, diabetes mellitus, age, and hepatic cirrhosis. Therefore, fluctuations in SHBG can lead to misinterpretations of the true, biologically available testosterone. With this understanding, current recommendations state that free or bioavailable testosterone, in addition to a total testosterone concentration threshold defines hypogonadism. The normal range can vary depending on the institution and patient population. As a general rule, the concentration at which there is a greater likelihood of symptoms occurring is <300 ng/dL. However, there are no definitive testosterone concentrations that increase the risk of adverse outcomes. Additionally, there is no well-accepted goal concentration that marks improved outcomes, further supporting the recommendation to reserve TRT for those with concurrent symptoms. The goal of TRT is to restore testosterone concentrations to a normal range while at the same time improving symptoms and increasing a patient’s quality of life.

To assist in ensuring an accurate diagnosis, the influence of circadian variations should also be considered. The highest concentrations of testosterone occur around 8 AM and the lowest around 8 PM. Therefore, it is recommended that both an initial and repeat serum TT concentration be measured in the morning. If an initial TT is low, a second TT measurement should be taken on another morning to confirm the low measurement. Men may lose these circadian patterns as they age. Therefore, the timing of measurement becomes less critical for an older patient, but as a general guideline, attempts should be made to obtain the measurement in the morning.

Once it is determined that a patient is a candidate for TRT based on symptoms and serum testosterone concentrations, the safety profile of TRT should be considered. Table 1 lists safety considerations for pa-

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**Box | Signs and symptoms of hypogonadism.**

- Reduced sexual desire (libido)
- Decreased energy or motivation
- Poor concentration and memory
- Weight loss
- Reduced muscular strength
- Breast discomfort, gynecomastia
- Low bone mineral density, low trauma fracture
- Hot flushes
- Low sperm count
- Depressed mood

---

**Table 1 | Safety considerations for patients with pre-existing comorbidities.**

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Safety Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Prostatic</td>
<td>TRT may lead to urologic symptoms, and should be discontinued if urethral obstruction develops in patients with BPH or in patients with a palpable prostate nodule or induration.</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>Breast cancer is a hormone-dependent cancer which may be stimulated during testosterone treatment. Currently marketed products list carcinoma of the breast as a contraindication.</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Testosterone may alter serum lipid profiles, but data are inconsistent. Supraphysiologic doses of nonaromatizable androgenic steroids appear to lower HDL. Conversely, a number of controlled studies that used physiologic replacement doses of testosterone showed minimal or no reductions in HDL with some actually showing reductions in total cholesterol.</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Testosterone therapy is not recommended in patients with uncontrolled or poorly controlled congestive heart failure. Fluid retention has been observed with testosterone therapy, which may exacerbate pre-existing heart failure. Importantly, a diagnosis of heart failure does not preclude a patient from using testosterone, but it is considered a precaution.</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Higher testosterone concentrations can stimulate erythropoiesis, reflected through increases in either hematocrit or hemoglobin. Elevation beyond a normal range may have coronary or cerebrovascular consequences and there appears to be a greater risk for erythrocytosis with injectable forms than with the topical preparations. However, both carry risk necessitating monitoring.</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>The causality between testosterone therapy and prostate cancer has not been definitively established. The prevalence rates for prostate cancer across a number of prospective studies in men receiving TRT appears to be similar to the general population. Product manufacturers list known or suspected prostate cancer as a contraindication for use.</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>TRT has been associated with exacerbation of sleep apnea. Although sleep apnea is not a contraindication for TRT, caution is warranted in patients with severe or untreated sleep apnea.</td>
</tr>
<tr>
<td>Sleep Apnea</td>
<td>Patients may require less insulin due to decreases in blood glucose caused by testosterone therapy and the positive correlation between testosterone concentrations and insulin sensitivity.</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td></td>
</tr>
</tbody>
</table>
tients with specific underlying comorbidities. TRT may alter these underlying diseases, and the added risk must be assessed before the initiation of therapy. Furthermore, associated laboratory parameters also require initial assessment and follow-up monitoring. Table 2 highlights recommended baseline laboratory monitoring and suggested timetables for follow-up.

Once the decision to start TRT has been made, the decision of which product to start is not straightforward and should be patient-centered. Patient preference can play a large role in choosing the most appropriate treatment option. Several different delivery systems of testosterone are available, including injections, transdermal systems, tablets, and buccal preparations. Although the therapeutic goals are the same for each product, the efficacy and safety of the different TRT products are not the same, nor is the complexity of use. The different TRT products are reviewed below and summarized in Table 3.

### Intramuscular Injection

Injectable testosterone is one of the most commonly used forms of TRT. The ester derivatives, testosterone cypionate (available in 100 and 200 mg/mL concentrations) and testosterone enanthate (available in 200 mg/mL concentration), are intramuscular (IM) preparations that have an increased lipophilicity when compared with the native testosterone molecule. The preparations are suspended in oil which prolongs the absorption and allows for a gradual release from the muscular tissue into the systemic circulation,10 which allows for a prolonged dosing interval of once weekly or once every two weeks. For some patients, this infrequent dosing interval can assist with adherence. Although the extended dosing interval of every 2 weeks may be more convenient for some patients, such dosing can lead to greater fluctuations between the peak and nadir concentrations.11 These peaks may be supraphysiologic and the trough concentrations prior to the next injection may be hypogonadal,12 which may be reflected in the patient’s clinical symptoms.1 One way to reduce the likelihood of this effect is to administer the injection once weekly as opposed to every two weeks. However, the Endocrine Society recommends both once weekly and every 2 week dosing frequencies.1 The recommended dose regimens for IM testosterone are 75-100 mg of either testosterone enanthate or testosterone cypionate once weekly, or 150-200 mg administered every 2 weeks.1

Side effects unique to the IM injectable testosterone include hypogonadal symptoms before the next injection, as well as hypergonadal symptoms such as aggression or irritability 1-3 days after an injection. There is also the possibility of an injection site reaction at the site of administration.1

A patient’s ability to self-administer IM TRT or ability to have someone else administer are important considerations with the injectable products. Patients may not feel comfortable injecting a dose on their own, and self-administration requires a patient to precisely draw up a dose. A solution for some patients is to have the injection administered by a health professional during a scheduled visit, which can improve adherence, take the burden away from the patient, and allow for closer monitoring for possible side effects.

Lastly, parenteral testosterone is one of the more affordable TRT options. Further, when administered by a health professional, the drug can be billed under a medical office co-pay. Partly owing to its low cost, IM TRT has been and will likely continue to be one of the more popular TRT options.

### Transdermal Gel

The transdermal testosterone gels are another TRT...
option and include AndroGel® (1%, 1.62%), AndroGel® Pump (1%, 1.62%), Fortesta™ (2%), and Testim® (1%). The testosterone is absorbed into the skin and provides a continuous delivery of testosterone over 24 hours. As opposed to the IM injection, the gel is administered once daily on the arms, shoulders, or abdomen, with the site of administration dictated by the specific product.13-15

The gel TRT products offer some unique advantages compared to the other products. The gels result in less skin irritation compared with the transdermal patch.16 Also, the pronounced peak and trough concentrations seen with the injectable preparations are not a concern with the once-daily administration of the gels. Dose adjustments can be easily managed with either an increase or decrease in the number of pump actuations.13 The burden of a once-daily application may affect some men, but if it is integrated as part of a daily routine, the frequency of application becomes more a matter of developing a habit.

When initiating treatment with transdermal gels, patients should be educated on risks of inadvertent transfer to others, especially women and children. The recommended application area is one that can be covered by a patient's shirt.13 Once dry, the application site should be covered and the patient should wash his hands. Children and women need to avoid unwashed or unclothed application sites. If direct skin-to-skin contact is anticipated, the application site should first be washed thoroughly with soap and water.13

Adverse effects of the transdermal gel products are similar across the different brands. These include emotional lability, contact dermatitis, prostate-specific antigen (PSA) elevations, hematocrit increases, headache and hypertension.13-15

**Transdermal Solution**

The transdermal solution (Axiron® 30 mg/90 mL) is similar to the transdermal gels, with the only differences being the method of application. The transdermal solution is applied to each of the axilla regions once a day.17 The same precautions apply with the transdermal solution, including the possibility of transfer to another person. Thus, the axilla should not be in direct contact with others immediately after the application when the product has not been allowed to dry. Patients should cover the application site with clothing after the solution has dried to minimize secondary exposure to others. If interpersonal contact is anticipated, the application site should always be washed prior to contact regardless of the length of time since the application.17
Implantable Pellet

Testosterone pellets (Testopel® 75 mg) are surgically implanted subcutaneously in either the lower abdomen or gluteus muscle and remain in the body for 3-6 months.21 The pellet serves as a depot which can maintain normal serum testosterone concentrations for months.21 The pellets are a long-acting testosterone treatment option which require an implantation procedure and no further patient adherence. The number of pellets that are inserted can vary depending on the desired serum concentrations. More than one implant is often administered at one time, with the standard dose being six to ten, 75 mg pellets implanted subdermally every 4-6 months.22

The pellets are another recommended initial treatment option according to the Endocrine Society.1 However, the burden of the surgical implantation can be a disadvantage for a patient. Additionally, pellet extrusion and infection are two side effects associated with the formulation.21 Its role in treating age-related male hypogonadism should be restricted to those men who already have established beneficial effects from testosterone replacement therapy.22

Oral Therapies

Oral forms of testosterone have been evaluated for the treatment of low libido and hypogonadism, but none are approved for use in the U.S. because of the high risk of hepatotoxicity.1 Adjusting therapy typically occurs two weeks to two months after therapy has started, depending on the product chosen. Table 4 summarizes the recommended dose adjustments for various products.

As stated above, the goals of testosterone therapy are to restore testosterone concentrations to a normal range to help improve symptoms and increase a patient’s quality of life. The following sections highlight the evidence for TRT in the improvement of commonly reported symptoms in hypogonadism.

Sexual Function

Erectile dysfunction (ED) and decreased libido can reduce quality of life. Men who have documented testosterone deficiencies and diminished libido may benefit from TRT, although the evidence supporting TRT for erectile dysfunction and sexual libido are mixed.
A 2007 meta-analysis of 17 randomized placebo-controlled trials with 862 participants was conducted to determine the effects of testosterone on sexual function in men with varying testosterone concentrations. In those trials that enrolled patients with low testosterone concentrations, the use of testosterone had a nonsignificant effect on satisfaction with erectile function (95% CI, -0.10 to 1.60), a significant effect on libido (95% CI, 0.40 to 2.25), and a nonsignificant effect on sexual satisfaction.23

In those trials that enrolled patients with low-normal to normal testosterone concentrations, testosterone caused a small statistically significant effect with erectile function (95% CI, 0.03 to 0.65), moderate nonsignificant effects on libido (95% CI, -0.01 to 0.83) and no significant effect on sexual satisfaction.23

The benefits from TRT for improving ED and sexual libido are mixed and can vary from patient to patient. The improvements in libido appear to be more consistent than improvements on erectile function,23 yet the overall impact on sexual function is still not clearly defined.

## Table 4 | Serum concentration measurements and corresponding dose adjustments.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Timing/Frequency of Measurements</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>testosterone cypionate or enanthate (injectable solution)</td>
<td>Measure midway between injections initially, and then periodically thereafter.</td>
<td>• Adjust dose or frequency if testosterone concentration is &lt;400 ng/dL or &gt;700 ng/dL.1</td>
</tr>
<tr>
<td>AndroGel® 1% (transdermal gel)</td>
<td>Measure morning serum testosterone concentration about 14 days after the start of therapy or after dose adjustments.</td>
<td>• Above normal range: ↓ dose daily; discontinue if consistently above normal at 50 mg daily. • Below normal range: ↑ dose from 50 mg to 75 mg or from 75 mg to 100 mg</td>
</tr>
<tr>
<td>AndroGel® 1.62% (transdermal gel)</td>
<td>Measure morning serum testosterone concentrations after 14 and 28 days of starting therapy or after dose adjustments and periodically thereafter.</td>
<td>• ↓750 ng/dL: ↓ dose by 20.25 mg daily • ≥350 ng/dL to ≤750 ng/dL: Maintain current dose • &lt;350 ng/dL: ↑ dose by 20.25 mg daily</td>
</tr>
<tr>
<td>Fortesta™ 2% (transdermal gel)</td>
<td>Serum testosterone concentrations can be measured 2 hours after application and after 14 and 35 days of starting therapy or dose adjustments.</td>
<td>• ≥2500 ng/dL: ↓ dose by 20 mg daily • ≥1250 to &lt;2500 ng/dL: ↓ dose by 10 mg daily • ≥500 and &lt;1250 ng/dL: Maintain current dose • &lt;500 ng/dL: ↑ dose by 10 mg daily</td>
</tr>
<tr>
<td>Testim® 1% (transdermal gel)</td>
<td>Measure morning serum testosterone concentrations approximately 14 days after initiation of therapy.</td>
<td>• Greater than normal range: ↓ dose; discontinue if consistently above normal at 5 g (50 mg testosterone) daily • Below normal range or lack of desired clinical response: ↑ dose from 5 g (50 mg testosterone) to 10 g (100 mg testosterone)</td>
</tr>
<tr>
<td>Androderm® (transdermal patch)</td>
<td>Measure morning serum testosterone concentrations (following application the previous evening) approximately 14 days after start of therapy or dose adjustments.</td>
<td>Initial: 4 mg daily (one 4 mg/day patch) • ↓930 ng/dL: ↓ dose to 2 mg daily (one 2 mg/day patch) • 400-390 ng/dL: Continue 4 mg daily • &lt;400 ng/dL: ↑ dose to 6 mg daily (one 4 mg/day patch and one 2 mg/day patch) Initial: 5 mg daily (one 5 mg/day patch or two 2.5 mg/day) • ↓1030 ng/dL: ↓ dose to 2.5 mg daily • 300-1030 ng/dL: Continue 5 mg daily • &lt;300 ng/dL: ↑ dose to 7.5 mg daily (one 5 mg/day and one 2.5 mg/day patch)</td>
</tr>
<tr>
<td>Axiron® (transdermal solution)</td>
<td>Measure serum testosterone concentrations 2-8 hours after applying Axiron® and at least 14 days after starting treatment or following dose adjustment.</td>
<td>• Consistently exceeds 1050 ng/dL at 30 mg: Therapy should be discontinued • ↓1050 ng/dL: ↓ dose from 60 mg to 30 mg • &lt;300 ng/dL: ↑ dose from 60 mg to 90 mg or from 90 mg to 120 mg</td>
</tr>
<tr>
<td>Striant® (buccal tablet)</td>
<td>Measure total serum testosterone 4-12 weeks after initiating treatment, prior to morning dose.</td>
<td>None recommended. If concentrations consistently exceed the upper limit of normal, a product switch or discontinuation should be considered</td>
</tr>
<tr>
<td>Testopel (Implantable pellet)</td>
<td>Measure testosterone concentrations at the end of the dosing interval.</td>
<td>Adjust the number of pellets and/or the dosing interval to achieve serum concentrations in normal range</td>
</tr>
</tbody>
</table>
**Depression**

The effects of TRT on depression are also inconsistent. A 2009 systematic review considered the impact of TRT on depression, and found that TRT resulted in a significant improvement on the HAM-D in depressed patients compared with placebo (p<0.0001). The effect remained consistent when evaluating the subgroup of men with hypogonadism (p<0.0001).24

In contrast to the positive results of the meta-analysis, other trials did not find any significant benefits of TRT on depression. In one such study, the safety and efficacy of 1% testosterone gel was evaluated for hypogonadal men older than 50 years of age who were already receiving antidepressants. Although a significant improvement in depressive symptoms was observed from baseline to week 12, there was not a significant difference when compared against the placebo-controlled group, suggesting that the apparent improvement with TRT was largely due to a placebo-effect.25

**Bone Mineral Density, Strength and Body Composition**

TRT has consistently demonstrated modest positive benefits on bone mineral density (BMD) in hypogonadal men.26-28 However, the effect of TRT on prevention of fractures is not known, and further studies are needed to assess TRT for the reduction in fracture risk.1

Improvements in body composition have been observed with testosterone therapy across multiple dosage forms. Specifically, changes in the amount of fat mass and fat-free mass as well as changes in muscular strength have been reported.16 In a systematic review done by the Endocrine Society, TRT was associated with a significantly greater increase in lean body mass (2.7 kg; 95% CI, 1.6 to 3.7) and a greater reduction in fat mass (-2.0 kg; 95% CI, -3.1 to -0.8) than placebo with nonsignificant overall body weight changes.20

**CONCLUSIONS**

The symptoms of hypogonadism in the aging male are legitimate concerns and can have impacts on the overall well-being for an individual with this condition. Male hypogonadism can be associated with a number of signs and symptoms, and TRT may play a role in alleviating these symptoms. TRT should be considered when an individual presents with symptoms consistent with hypogonadism, and a TT concentration measurement confirms definitively low concentrations. With testosterone continuing to be the mainstay of therapy, the focus now revolves around making an appropriate drug formulation choice based on cost, side effects, and patient preferences. Practitioners are afforded many TRT options, and the decision to treat and what to treat with should be made in conjunction with the patient, recognizing that patients are frequently bombarded with disease awareness campaigns (i.e., “low T”) from the makers of TRT products. Perhaps more so than other diseases seen in an outpatient setting, patient input is an important factor for product choice. The long-term benefits and risks of TRT still require further assessment, but drug therapy options continue to grow and may be viable options for the treatment of age-related male hypogonadism.

**References**

15. TESTIM 1% [package insert]. San Antonio, TX: DPT Laboratories; 2009.

Comparative Efficacy and Safety of the GLP-1 Agonists for Treatment of Type 2 Diabetes Mellitus

Daniel Cho, PharmD candidate

In 2010, 25.8 million people in the United States, or 8.3% of the population, suffered from diabetes.1 Diabetes is the seventh leading cause of death in the U.S., and is a major cause of many complications including cardiovascular disease, kidney failure, nontraumatic lower-limb amputations, and new cases of blindness.1 Despite many advances in therapeutic options for treatment of diabetes, most patients still fail to reach optimal glycemic control, and many long-term treatment options are often associated with hypoglycemia or weight gain. Glucagon-like peptide-1 (GLP -1) agonists are a newer class of medications, used in the treatment of type 2 diabetes, which have demonstrated efficacy in improving glycemic control, and weight loss.2 The GLP-1 agonists available in the U.S. include exenatide and liraglutide. Immediate-release (IR) exenatide was granted an FDA-approved indication in 2005 for the treatment of type 2 diabetes under the trade name Byetta®.3 An extended-release (ER) formulation of exenatide, which is administered once weekly, was later granted an approved indication by the FDA in 2012 under the trade name Bydureon®.4 The most recently marketed GLP-1 agonist, liraglutide, which was granted an approved indication in 2010, is available under the trade name Victoza®.5 The objectives of this article are to compare the pharmacology, pharmacokinetics, efficacy, safety, and costs of the three GLP-1 agonists currently available in the U.S.
The GLP-1 agonists bind to and activate the human GLP-1 receptor and improve glycemic control through several mechanisms, including enhancement of glucose-dependent insulin secretion by the pancreatic β-cells, suppression of elevated glucagon secretion during periods of hyperglycemia, and slowing of gastric emptying, thereby reducing the rate at which meal-derived glucose appears in the circulation. GLP-1 agonists also improve glycemic control by reducing fasting and post-prandial glucose concentrations.

Liraglutide achieves peak plasma concentrations at 8 to 12 hours after subcutaneous administration. The mean volume of distribution is approximately 13 L. Unchanged liraglutide is not detected in the urine or feces indicating that liraglutide is completely metabolized and degraded in the body. Furthermore, only small quantities of metabolites are excreted in the urine (6%) or feces (5%). The mean clearance of liraglutide is approximately 1.2 L/hour with a half-life of approximately 13 hours. Limited evidence exists for demonstrating safety of liraglutide in patients with renal or hepatic dysfunction; therefore, liraglutide should be used with caution in these patients, but no dose adjustments are required.

**COMPARATIVE EFFICACY OF GLP-1 AGONISTS**

No long-term studies have assessed important health outcomes and safety of GLP-1 agonists and they are not recommended for use as monotherapy, according to the AACE/ACE guidelines. Additionally, these agents target post-prandial glucose levels primarily, while the primary target for initial therapy should focus on fasting glucose.

Three head-to-head trials have been published comparing the efficacy and safety of the different GLP-1 agonists although no single study compares all three agents directly. The three comparative trials are DURATION-5 (exenatide once weekly versus exenatide twice daily), LEAD-6 (liraglutide versus exenatide twice daily), and DURATION-6 (exenatide once weekly versus liraglutide). These trials are summarized in Table 1 and the comparative efficacy and tolerability...
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size &amp; Study Design</th>
<th>Inclusion Criteria</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DURATION-5</strong></td>
<td>N = 252</td>
<td>≥18 years old with type 2 diabetes</td>
<td>Exenatide 2 mg once weekly for 24 weeks vs. Exenatide 5 mcg twice daily for 4 weeks followed by 10 mcg twice daily for 20 weeks</td>
<td>Change in A1c from baseline and weight loss</td>
<td>At 24 weeks, once weekly exenatide produced significantly greater A1c changes compared to twice daily exenatide (-1.6% vs. -0.9%, respectively; p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>LEAD-6</strong></td>
<td>N = 464</td>
<td>18-80 years with type 2 diabetes</td>
<td>Liraglutide 1.8 mg once a day vs. exenatide 10 mcg twice a day</td>
<td>Change in A1c and weight loss from baseline to week 26</td>
<td>Liraglutide reduced mean A1c compared to exenatide (-1.12% vs. -0.79%; p&lt;0.0001)</td>
</tr>
</tbody>
</table>

| **DURATION-6** | N = 911 | >18 years old with type 2 diabetes | Liraglutide 1.8 mg once a day vs. exenatide 2 mg once weekly | Change in A1c at week 26 from baseline and weight loss | A1c reduction was no different between liraglutide and exenatide group (-1.48% vs. -1.28%; p=NS) |
|                |         | Suboptimum glycemic control despite lifestyle modification |                                 |                                                        | Patients taking liraglutide showed greater reductions in body weight compared to exenatide (-3.57 kg vs. -2.68 kg) |
are described in Table 2.

**SAFETY & TOLERABILITY**

The GLP-1 agonists are generally well-tolerated and all three agents have similar adverse event profiles, with some modest differences between agents. The most common adverse events seen in clinical trials were gastrointestinal in nature, including nausea, diarrhea, and vomiting. Nausea was generally graded mild-to-moderate in severity, peaked during the initial eight weeks of therapy, and subsided with continued use. Starting therapy with a low dose and increasing the dose over a few weeks can help reduce the likelihood and severity of nausea. Nausea occurring after the maximum daily dose is reached should prompt a dose-reduction. Administering the agent immediately before or during, but not after, a meal may also reduce the likelihood and severity of nausea. Other tips for management of nausea include eating smaller portions and reducing the fat content of meals.

Exenatide ER and liraglutide are associated with black box warnings for risk of thyroid C-cell tumors. These agents have caused dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in rats. Whether thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), would occur in humans using these agents is not known; however, use of ER exenatide and liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). These risks have not been observed in patients treated with exenatide IR.

All three available GLP-1 agonists have been associated with pancreatitis. Patients should be observed carefully for signs and symptoms of pancreatitis, including persistent, severe abdominal pain that sometimes radiates to the back. If pancreatitis is suspected, the GLP-1 agonist should be discontinued and should not be restarted if pancreatitis is confirmed. Other anti-diabetic therapies should be considered in patients with a history of pancreatitis.

**Costs**

Relative to other anti-hyperglycemic agents, the GLP-1 agonists are considerably more expensive owing to their brand-name only availability. The average costs of the three GLP-1 agonists available are shown in Table 2.

**CONCLUSIONS**

While the GLP-1 agonists are not considered first line therapies for diabetes, exenatide (IR and ER) and liraglutide can provide an additional A1c lowering of approximately 0.85% to 1.44% when used in combination with oral anti-diabetic agents, such as metformin, a sulfonylurea, basal insulin, a thiazolidinedione, or a combination of metformin and either a sulfonylurea or a thiazolidinedione. Nausea and vomiting are common side effects with GLP-1 agonists, but may be transient and can be lessened by adjusting administration routines, using slow titrations, or choosing GLP-1 agonists with a longer half-life. Additionally, the GLP-1 agonists are an appealing choice for many patients because they can cause weight loss, up to an average of 2.14 to 3.41 kg, as opposed to the weight gain associated with most other anti-diabetic agents.

**REFERENCES**


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**Table 2 | Mean A1c lowering, weight loss, gastrointestinal adverse events, and costs for GLP-1 agonists**

<table>
<thead>
<tr>
<th>GLP-1 agonist</th>
<th>Mean A1c Lowering</th>
<th>Mean Weight Loss</th>
<th>Nausea</th>
<th>Diarrhea</th>
<th>Vomiting</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide twice daily</td>
<td>0.85%</td>
<td>2.14 kg</td>
<td>31.5%</td>
<td>8%</td>
<td>9.4%</td>
<td>$393.12</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>1.3%</td>
<td>3.41 kg</td>
<td>23%</td>
<td>12.5%</td>
<td>8.5%</td>
<td>$452.72</td>
</tr>
<tr>
<td>Exenatide once weekly</td>
<td>1.44%</td>
<td>2.5 kg</td>
<td>11.5%</td>
<td>7.5%</td>
<td>4.4%</td>
<td>$423.70</td>
</tr>
</tbody>
</table>