Onglyza and Where It Fits into Current Treatment of Diabetes Mellitus
Kate Choiniere, PharmD

**Short answer:** Saxagliptin (Onglyza™) is an oral, once-daily DDP-IV inhibitor (like sitagliptin (Januvia®)) and can be used as monotherapy or as adjunctive therapy in the treatment of type II diabetes. It is more effective for lowering post-prandial BG than fasting BG, and lowers A1c by approximately 0.6 percentage point. Keeping price (brand-only, approved in 2009) and lack of long-term safety data in mind, it could be chosen for a patient struggling with post-prandial peaks and who has not reached goal with metformin alone. It has not been studied in conjunction with insulin.

**Drug class:** dipeptidyl peptidase IV (DDP-IV) inhibitor

**Mechanism of action:** inhibits DDP-IV, which increases duration of active incretin levels (e.g. GLP-1, which is released in response to meals), which regulate glucose homeostasis by increasing insulin synthesis and release, and by decreasing glucagon secretion (decreases gluconeogenesis by the liver)

**Approved indication:** type II diabetes mellitus as monotherapy or adjunct therapy to other medications; has not been studied in combination with insulin

**Dosage & administration:** 2.5-5mg orally daily without regard to meals. For CrCl ≤ 50: 2.5mg daily (post-hemodialysis, if applicable)

**Dosages available:** 2.5, 5mg tablets

**Contraindications:** none

**Side effects:**
- <10% incidence unless otherwise noted: peripheral edema (increased risk if used with thiazolidinedione), headache, hypoglycemia

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**UW Ambulatory Care & Community Pharmacy Residency Programs**
- Bartell Drugs
- HealthPoint
- QFC
- Tulalip
- Valley View
(increased risk if used with secretagogues; 15%), gastrointestinal upset, urinary tract infections, lymphopenia, sinusitis, hypersensitivity reactions (e.g. urticaria, facial edema; 2% incidence)

- **<1% incidence**: increase in serum creatinine, creatine phosphokinase, idiopathic thrombocytopenic purpura, rash

**Pharmacokinetics**

- Metabolism: 3A4 (major, to active metabolite), P-gp
- Duration of effect: 24h

**Price**: 2.5mg or 5mg tablets #30 = $203.09 (per www.drugstore.com)

**Place in therapy**: Saxagliptin has been studied as monotherapy and as adjunctive therapy to metformin, glyburide, pioglitazone, or rosiglitazone. It has a greater effect on post-prandial blood glucose than fasting blood glucose. It reduces HgA1C by approximately 0.6% as either monotherapy (vs. placebo) or as adjunctive treatment with metformin, glyburide, pioglitazone, or rosiglitazone. DDP-IV inhibitors are a 2nd-line option (after metformin) per the Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

**References**:
3. Woo Y; CDA 2008 Clinical Practice Guidelines Steering Committee. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the
Liraglutide injection (Victoza®) - Carmela Andrada, PharmD

Short Answer:
Liraglutide (Victoza®) is a once-daily subcutaneous injection, glucagon-like peptide-1 (GLP-1) receptor agonist. It is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 DM. Consider use of liraglutide as add-on therapy to oral diabetic agents, particularly in patients with elevated post-prandial blood glucose levels, for weight loss in obese patients close to glycemic goals, and as an alternative to sulfonylureas in patients at high risk of hypoglycemia. Liraglutide is associated with decreased fasting blood glucose (FBG) as well. Advantages over exenatide (Byetta®) include once-daily dosing without regard to renal function and meals, slightly higher decrease in HbA1c from baseline (-1.1 versus -0.8%, respectively), and decreased incidence of nausea over time. Liraglutide is costlier than exenatide and long-term safety data has yet to be evaluated. Combination insulin therapy and liraglutide are currently being studied.

Indications and mechanism of Action
Liraglutide (Victoza®) is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 DM. It mimics native GLP-1, stimulating insulin release, decreases glucagon secretion in a glucose-dependent fashion, delays gastric emptying, and increases satiety.

Dosage and Administration
Liraglutide is administered once daily, regardless of meals via injection in the abdomen, upper arm, or thigh. Initial dose is 0.6 mg daily for 1 week and increased to 1.2 mg thereafter. If glycemic control is suboptimal, the dose may be increased to 1.8 mg. No dosage adjustments are necessary in renal and hepatic impairment, but limited information is available in these patient populations. Liraglutide is available as a pre-filled, multi-dose pen that delivers doses of 0.6mg, 1.2mg, or 1.8mg (6mg/ml, 3ml).

Pharmacodynamics/Pharmacokinetics
Slow absorption of subcutaneous liraglutide results in a peak plasma concentration 8 to 12 hours after administration. Its time to peak and long half-life (about 13 hours) allow for once daily dosing. Liraglutide is endogenously metabolized by dipeptidyl peptidase IV (DPP-IV) and other peptidases and excreted in the urine (6%) and feces (5%) as metabolites.
Adverse Effects
Common adverse effects include headache, nausea, and diarrhea. However, slow titration of liraglutide during the first week of therapy minimizes gastrointestinal side effects. Severe hypoglycemia may occur when used with insulin secretagogues/sulfonylureas. Consider dose adjustment to reduce risk. Liraglutide is contraindicated in patients with personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia (MEN) syndrome type 2. Rare cases of pancreatitis were reported in liraglutide clinical trials. Caution is advised in patients with a history of pancreatitis. Discontinue liraglutide if pancreatitis occurs.

Storage and Cost
Store liraglutide in the refrigerator 36°F to 46°F (2°C to 8°C) if unused. Pen that is in use stored at room temperature (59°F to 86°F) is good for 30 days. A 30-day supply of liraglutide 1.2mg or 1.8mg daily costs $279.97 or $399.98, respectively.

Place in Therapy
Liraglutide has been studied as monotherapy in comparison to placebo, glimepiride, and sitagliptin. It has also been studied as add-on therapy to metformin plus either glimepiride, rosiglitazone, or sitagliptin. Overall, liraglutide reduced HbA1c by approximately -1.0 to -1.5 percentage points and lowered FBG by about -15 to -43 mg/dL from baseline across trial. Monotherapy led to a 2.5 kg reduction in weight. Consider addition of liraglutide after failure of metformin and/or sulfonylureas. Reduction of sulfonylurea dose may be needed to minimize the risk of hypoglycemia. Liraglutide may confer added benefit in patients with elevated post-prandial sugars, obese patients close to glycemic goals needing weight loss, or as an alternative to sulfonylureas in patients at high risk of hypoglycemia. Combination insulin therapy and liraglutide are currently being studied.

Exenatide (Byetta®) is the other GLP-1 agonist currently available on the market. Advantages of liraglutide include once-daily dosing without regard to meals or renal function and slightly higher reduction in A1c compared to meals or renal function and slightly higher reduction in A1c compared to exenatide (1.1% vs. 0.8% respectively, as add-on therapy to oral antidiabetic agents). There is no significant difference in weight loss between both GLP-1 agonists (-3.24 kg versus -2.87 kg). Liraglutide is higher in cost compared to high dose exenatide. A 30-day supply of exenatide 5mcg or 10mcg twice daily costs $264.63 or $271.98, respectively. A once-weekly dosing of exenatide is currently being studied in clinical trials.

References:
Dietary Supplements Blood Sugar Control in Patients with Diabetes - Jessica Sipe, PharmD

Evidence-Based Answer

The short answer is maybe. The long answer is that many natural medicines have been tried for diabetes and blood sugar control and many of them have real pharmacological effects that might eventually prove to be beneficial.¹ But so far many of these products lack the high-quality evidence of safety and effectiveness needed to recommend them for long-term use for type 2 diabetes or its complications.¹² It is very important not to replace conventional medical therapy for diabetes with an unproven CAM therapy. In addition, it is wise to advise patients not to combine hypoglycemic natural medicines with conventional diabetes medicines. The biggest concern is when natural medicines with hypoglycemic activity, due to insulin-like effects, are combined with conventional drugs with hypoglycemic effects. Patients should be counseled that these natural medicines can have real drug-like effects and to monitor their blood glucose closely if they try any of them.¹²

A few products are worth considering. Fibrous foods can be safely recommended. There is not a lot of evidence to support any one specific fiber product (psyllium, oat bran, soy, etc), but most experts agree that a diet consisting of 20-50 grams of fiber daily is beneficial.¹ Considering that most Westerners do not get adequate fiber in their diet, increasing dietary fiber could have many benefits, one of which is decreased blood glucose levels. Chromium might be worth a try short-term for some patients with a known deficiency.¹²³ Once the deficiency is corrected, the supplement should be discontinued. In addition to fibrous products and chromium, a few of the more common supplements touted to improve blood sugar are summarized below. Keep in mind that many other products are also hyped as natural “cures” for diabetes, but that evidence for their efficacy and safety is nominal at best.

Fiber products (Oat bran, guar gum, soy, blond psyllium, glucomannan, and others)¹²

Dose: varies depending on component. Research suggests that 25-35g of fiber (at least 20-30% soluble fiber) can lower blood glucose, decrease A1c and have beneficial effects on lipid levels.

Possible MOAs:
- Soluble fiber products increase the viscosity of the intestinal contents, slow gastric emptying time, and act as a barrier to diffusion. When these fibrous products are consumed in conjunction with a meal, they can slow the absorption of glucose and reduce postprandial blood glucose levels.
- Insoluble fiber delays glucose absorption and may increase insulin sensitivity.
Pearls:
- Advise patients with low fiber intake to gradually increase fiber over several weeks to avoid GI side effects.
- Ideal diets and supplements should have ~3:1 insoluble:soluble fiber ratio.
- Fiber can decrease the oral absorption of drugs. Tell patients to take medication either one hour before or four hours after taking a fiber supplement.
- The Natural Medicines Comprehensive Database (NMCD) lists fiber products as “likely safe and possibly effective.”

Chromium\textsuperscript{1,2,3}
Dose: 200-1000 mcg daily
- Chromium deficiency is associated with some of the features of diabetes: impaired glucose tolerance, hyperglycemia, glycosuria, a decrease in the number of insulin receptors, poor insulin binding, and neuropathy.
- Some evidence shows that taking chromium picolinate orally can decrease fasting blood glucose, insulin levels, and glycosylated hemoglobin (HbA1c) and increase insulin sensitivity in people with type 2 diabetes

Possible MOAs:
- Chromium is necessary for both normal insulin binding and insulin receptor activity.
- Chromium may activate insulin receptor kinase activity and inhibit insulin receptor tyrosine phosphatase, leading to increased phosphorylation of the receptor and increased insulin sensitivity.

Pearls:
- The ADA only recommends chromium for diabetics with chromium deficiency.

- Patients with renal disease should avoid chromium supplements; high doses may increase the risk of interstitial nephritis and tubular necrosis.
- The NMCD lists chromium as “possibly safe and possibly effective.”

American Ginseng\textsuperscript{1,2,4}
Dose: 3-9g up to 2 hours before a meal (doses above 3g don’t seem to be more effective)
- Clinical trials show that taking American ginseng 3 grams up to 2 hours before a meal can significantly reduce postprandial blood glucose.

Possible MOAs:
- The active components in ginseng are called ginsenosides, which are thought to decrease insulin resistance and improve insulin sensitivity.

Pearls:
- The glucose lowering effect of ginseng may vary among preparations because of variations in the concentration of ginsenosides.
- Patients on warfarin should not take ginseng; it can significantly reduce INR.
- Avoid confusion with other types of ginseng (Siberian, Panax). Panax ginseng may also be effective to lower blood sugar, but Siberian ginseng is not.
- The NMCD lists American ginseng as “possibly safe and possibly effective.”
Cinnamon\textsuperscript{1,2,5}

Dose: 1-6g of cassia cinnamon bark, usually in capsule form

- Although initially promising as an agent to lower both blood glucose and lipid levels, a recent meta-analysis suggests that the use of cinnamon did not significantly alter HbA1C, fasting blood glucose, or lipid parameters in patients with type 1 or type 2 diabetes.

Possible MOAs:

- The polyphenols (such as hydroxycalcone) may increase phosphorylation of the insulin receptor, thus increasing insulin sensitivity.
- Cinnamon extracts may also increase glycogen synthesis and increase glucose uptake into cells

Pearls:

- Cinnamon has a high coumarin content. The main concern for the coumarin in cinnamon is potential hepatotoxicity, although increased risk of bleeding should also be considered. Patients with liver disease should not take high doses of cinnamon.
- Cinnamon may decrease the absorption of tetracyclines.
- The amount of cinnamon in the typical diet will not have an effect on lipids or blood sugar.
- The NMCD lists cinnamon as “likely safe with insufficient clinical evidence.”

References:

Do SSRIs contribute to bone loss? – Amber Burdeau, PharmD

Evidence-Based Answer:

There are a few large observational studies that have evaluated the role of serotonin in bone metabolism; the exact role that serotonin plays in bone metabolism has not been determined. Large prospective trials are needed to determine the relationship between antidepressants and bone loss. The risks and benefits need to be balanced in treating depression with an agent that acts on serotonin, especially in the patients already at risk for fracture. The decision to use either an SSRI verse TCA verse trazodone should not be guided by current studies since they do not prove causation. Patients need to be counseled on fall prevention, adequate calcium and vitamin D supplementation, and smoking cessation to prevent fracture. A patient at risk for fracture, currently taking an agent that acts on serotonin, should have a bone mineral density test to monitor their risk for fracture and to determine if another antidepressant agent should be used.

Long-term use of selective serotonin inhibitors (SSRI) has been shown to be associated with bone loss and increased risk of fracture.¹ To date there has not been any prospective, double-blind, placebo controlled trials that have evaluated the association to prove causality. The studies that have been conducted are large observational studies. In these studies both SSRIs and tricyclic antidepressants (TCAs) have been associated with an increased risk of fragility fracture. There has also been large cross-sectional and prospective cohort studies showing that use of SSRIs, but not TCAs, has been associated with reduced bone mineral density in elderly men and increased rates of bone loss at the hip in elderly women.¹

TCAs have been known to be associated with fracture due to their adverse effects, including sedation and postural hypotension, which increase risk of falls.¹ The association with SSRIs and fracture is thought to be through serotonin’s direct effect on osteoclast activity leading to increased bone resorption, although studies regarding this are preliminary.² Studies are investigating how serotonin (5-HT) plays a role in regulating osteoclast differentiation and potentiation of osteoclast formation.² This may lead to an explanation of serotonin’s role in bone formation and if there is a dose response relationship with serotonin antagonists and decreased bone density.
Tricyclic antidepressants decreased reuptake of norepinephrine and serotonin.\(^3\) Amitriptyline appears to exert effects on both norepinephrine and serotonin. Amitriptyline is metabolized to nortriptyline, which accounts for most of the norepinephrine-reuptake inhibition after amitriptyline administration. Nortriptyline itself also possesses antidepressant activity. The hydroxy metabolites of amitriptyline are active as well. Varying degrees of sedation can be produced, and the seizure threshold can be lowered. Amitriptyline possesses strong anticholinergic activity. Cardiac dysrhythmias can result from the direct quinidine-like effect on cardiac function combined with anticholinergic activity and norepinephrine potentiation. Patients need to be warned about the side effects to TCAs, especially the elderly.\(^3\) There have not been any studies that have evaluated whether or not trazodone causes bone loss. Although, trazodone has a similar mechanism of action as SSRIs in that it inhibits the reuptake of serotonin, it is less potent.\(^4\) At high doses, 6 – 8 mg/kg, trazodone appears to act as a serotonin agonist. At low doses, 0.05 – 1 mg/kg, it appears to antagonize serotonin. The antidepressant actions of trazodone are believed to be due to blocking the reuptake of serotonin at the presynaptic neuronal membrane. Trazodones sedative effect is believed to be produced by the alpha-adrenergic blocking action and modest histamine blockade. Total sleep time is increased, but unlike the tricyclics, trazodone does not affect stage 4 sleep.\(^4\)

References:
Evidence-Based Answer:

While plasma CoQ10 level is shown to be reduced by HMG-CoA reductase inhibitors and increased by CoQ10 supplementation, no correlation between CoQ10 levels and myopathic symptoms have been consistently demonstrated. Therefore, CoQ10 supplementation does not provide definitive prevention of or reduction in myopathic symptoms associated with statin therapies.

Statin-associated myopathy is hypothesized to be a result, in part, of mitochondrial dysfunction due to inhibition of HMG-CoA reductase, which blocks downstream production of CoQ10, a ubiquinone involved in electron transport during oxidative phosphorylation in mitochondria and antioxidant activities.\(^1\)\(^,\)\(^2\) A randomized, double-blind pilot study examined the effect of CoQ10 supplementation on 32 patients treated with statins and reported symptoms of muscle pain with or without muscle weakness and fatigue.\(^3\) Eighteen patients were randomized to CoQ10 100 mg/day and 14 patients to vitamin E 400 IU/day for 30 days. Vitamin E was chosen to control for the antioxidant actions of CoQ10. Myopathic pain was evaluated before and after supplementation using the Brief Pain Inventory questionnaire. Four pain intensity scores and seven pain interference scores from the questionnaire were averaged into the Pain Severity Score (PSS) and the Pain Interference Score (PIS), respectively. Plasma creatinine kinase (CK) and fasting plasma lipid profile were measured before and after the 30-day intervention. In the CoQ10 group, PSS decreased 40±11% (5.00±0.34% at baseline versus [vs.] 2.97±0.48 at 30 days, p<0.001) and PIS improved by 38±14% (4.31±0.50 at baseline vs. 2.82±0.61, p<0.02). In contrast, no significant changes in PSS or PIS were observed for the vitamin E group. Change in PSS from baseline in the CoQ10 group was significantly different from that for the vitamin E group (-2.05±0.44 vs. +0.34±0.33, p<0.001).

Despite subjective pain improvement, however, plasma CK concentrations before and after supplementation with either CoQ10 or vitamin E did not change. Additionally, no correlation between pain score and plasma CK concentration was observed. Two limitations exist for this study. First, the study lacked placebo control, making subjective pain assessments difficult to interpret. Second, while the CoQ10 and vitamin E groups had similar statin treatments, the medications and doses were not standardized, which may have contributed to a higher variability among outcome measures and difficulty in detecting significant findings.
A randomized, double blind, placebo-controlled study examined the effect of CoQ10 supplementation in 49 Japanese hypercholesterolemic patients treated with atorvastatin. After a four-week dietary lead-in period, patients were given atorvastatin 10 mg/day for 16 weeks and randomized to placebo (n=25) or CoQ10 100 mg/day (n=24) for 12 weeks. In the CoQ10 group, plasma CoQ10 levels at weeks four, eight, and twelve significantly increased compared to baseline (2.402±0.825, 2.402±0.738, 2.531±0.874 vs. 1.113±0.444, respectively, p<0.001). Plasma CoQ10 levels for placebo group at weeks four, eight, and twelve significantly decreased compared to baseline (0.731±0.201, 0.711±0.256, 0.691±0.234 vs. 1.180±0.282, respectively, p<0.001), and these values were significantly different from the plasma CoQ10 levels of the CoQ10 group (p<0.0001). At week sixteen, the plasma CoQ10 level of the intervention group significantly decreased (0.866±0.430 vs. 1.180±0.282 at baseline, p=0.05) but was similar to the CoQ10 level of the placebo group (0.762±0.325). No serious adverse events or symptoms of myalgia were reported. Given the low dose of atorvastatin used, the small number of subjects without existing myopathy, and the relatively low probability of myopathy, it was likely that the study sample was not large enough to detect myopathy symptoms that may exist.

Another double blind, placebo-controlled pilot study in 44 patients with self-reported myalgia examined the effect of CoQ10 supplementation on simvastatin tolerance and myopathic symptom improvement. After a two-week washout period of CoQ10 and lipid modifying therapies, patients were stratified into severe myalgia (inability to tolerate simvastatin 20 to 40 mg/day within one month of initiating therapy, n=19) and moderate myalgia (development of myalgia symptoms at doses ≥20 mg/day after one month of therapy, n=25). Within each stratum, patients were randomized to CoQ10 200 mg/day or placebo for 12 weeks. Dose of simvastatin was increased from a starting dose of 10 to 20 mg/day and to 40 mg/day at weekly intervals. Patients recorded intensity of daily myalgia on a visual analogue scale and documented the number of sites affected. Primary outcomes were the number of patients who tolerated simvastatin 40 mg/day at 12 weeks, the number of patients remaining on simvastatin therapy, and change in myalgia score. Comparing CoQ10 group to placebo group, no significant difference was observed for the amount of people tolerating simvastatin 40 mg/day (73% vs. 50%, p=0.34) or remaining on therapy (73% vs. 82%, p=0.47). Change in myalgia scores expressed as a median for CoQ10 and placebo groups were 6.0 and 2.3 millimeters, respectively. The slight increase in myalgia scores in both groups are significant compared to baseline (p=0.001), but are not significant between the two groups, for the study was powered to detect a nine millimeter different between groups. Plasma CoQ10 levels increased with CoQ10 supplementation (131%, p<0.001) but decreased with placebo (-34%, p<0.001).

References:
Warfarin interaction with statin and SSRIs - Valerie Tran, PharmD

Evidence-Based Answer:

From the drug interactions standpoint, it seems that citalopram is a safer alternative for elderly patients on concomitant SSRI/warfarin therapy due to CYP-P450 pathway and side effect profile. As an alternative, atorvastatin seems to be a better drug choice that will avoid an INR increase.

Warfarin vs. fluoxetine

Lexi-comp drug interaction details case reports of increase INR with fluoxetine (4-7 fold) and paroxetine with association to bleeding.¹ These interactions seem to be related to the CYP isoenzymes, specifically 1A2, 2C9 and 2C19 as well as 3A4. It further states that The Psychiatry journal reports that sertraline and citalopram are safer and poses less risk for drug interactions due to their limited inhibition capabilities of the CYP enzymes (sertraline and citalopram predominantly impacts 2D6 pathway, and seems to have less risk of warfarin interaction from a clinical standpoint).²

Furthermore, elderly patients are at increased risk for falls from anticholinergic activity. Facts and Comparisons show sertraline with higher anticholinergic profiles (6-17% dizziness, 12-28% insomnia, 10-16% fatigue, versus few reports of dizziness for citalopram, and 15%, 5%, respectively).³ (pg 1382). Data seems to point towards citalopram with the fewest interactions and favorable side effect profile for the elderly.³

Warfarin vs. simvastatin

Case reports show that simvastatin may increase warfarin concentration and response.⁴ Both share similar CYP-3A4 pathways, and upon initiation, discontinuation, or changes in dose, the INR is affected. Pravastatin may have modest effect on INR, though reportedly not greater than simvastatin. Atorvastatin appears to have no clinical activity on warfarin. This alternative seems to be a safer choice for patients on concomitant warfarin therapy.⁴

References: