CASE REPORT

Saxenda in the Management of Obesity in a Type 2 Diabetes Mellitus Patient: A Case Report

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ABSTRACT

Obesity is a major public health concern in all developed countries and is an emerging epidemic in developing countries. Obesity is associated with an increased risk of death and major well-known comorbidities. Lifestyle interventions are the first-line treatment for most overweight and obese patients, but most people failed to achieve and maintain their weight loss. For them, the introduction of pharmaceutical aids may be suitable. In this case report, we will use Saxenda as an adjunct to lifestyle interventions in achieving and sustaining weight loss and improving comorbid conditions. In our 52 year-old patient, the addition of Saxenda has contributed to a total weight loss of > 10% of his initial body weight. We also noted a great improvement of his T2DM and a normalization of his metabolic profile. The most common adverse effects were nausea; it occurred early in the treatment phase and was easily manageable. No hypoglycemic episodes have occurred. Therefore, Saxenda has a positive benefit/risk ratio in this patient for weight loss management.

Key words: Cardiovascular disease, glucagon-like peptide 1 receptor agonist, obesity, pharmacologic therapy, saxenda, type-2 diabetes mellitus, victoza, weight loss

INTRODUCTION

Obesity is a major public health concern in all of the developed countries and is an emerging epidemic in the developing countries.[1] Many leading institutions such as the American Medical Association, the National Institutes of Health, the Obesity Society, and the American Association for Clinical Endocrinology concur that obesity is a chronic disease that necessitates relevant efforts in prevention and management.[2] Obesity is associated with an increased risk of death and major comorbidities including hypertension, hyperglycemia (pre-diabetes and type 2 diabetes mellitus [T2DM]), dyslipidemia, various types of cancer, obstructive sleep apnea (OSA), and atherosclerosis[3] as well as a reduced life expectancy.[4,5] Obesity can also reduce the quality of life.[6] Unfortunately, the risk of obesity-related complications and comorbidities increases with increasing body mass index (BMI). Another important concern is that childhood overweight or obesity is also an independent predictor for obesity in adulthood and its associated comorbid conditions. Obesity is also rapidly increasing in pediatric populations leading to the risk of having more obesity in adults.[7,8]

On the other hand, a modest weight loss of 5–10% has been shown to have significant health benefits in terms of improving glycemic control, reducing progression to 2DM, and improving comorbidities such as hypertension, dyslipidemia, and OSA.[9,10] Moreover, these weight loss percentages have become the main goal in the management of obesity.

It is well-known that lifestyle interventions in the form of diet, regular moderate-to-intense physical activity, and behavioral changes are the first-line treatment, but most people with obesity have difficulties to achieve and maintain their weight loss and often fail.[10-15] For them, the introduction of pharmaceutical aids may be highly appreciated.

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In this case report, we will use Saxenda as a valuable adjunct to lifestyle intervention in achieving and sustaining clinically relevant weight loss, improving comorbid conditions, and facilitating healthier lifestyle habits. Few other weight loss medications are currently available, and most of them are not as successful as expected.[10] Below, we will briefly discuss their pros and cons to guide the readers in the selection of the most appropriate pharmaceutical aids to facilitate their weight loss. In particular, pharmacologic therapy may often be associated with safety concerns, undesirable side effects, or offer no improvement in cardiovascular (CV) risk factors.[10] That is why, it is particularly important to select a pharmaceutical aid with limited side effects and that we can use in the maintenance phase of weight loss, i.e., a pharmaceutical aid that we can use safely in long term.

Gastric banding and gastric bypass surgery are other current therapies shown to be effective for weight reduction in adult subjects with obesity.[16,17] Interestingly, the different types of surgery have been shown to have various effects on gastrointestinal incretin hormones such as increasing glucagon-like peptide-1 (GLP-1), which is involved in the mechanism of action of Saxenda and thereby ameliorates weight loss and T2DM.[15] However, gastric bypass surgery and banding are invasive methods with a number of potential complications both during and after surgery and are often not accessible for many patients.[16,17]

Liraglutide is a derivative of GLP-1 sharing 97% amino acid sequence homology with its parent molecule.[11-12,15] GLP-1 is a polypeptide incretin hormone secreted by the L-cells of the gastrointestinal tract in response to nutrients in the lumen. It causes glucose-dependent stimulation of insulin secretion,[11,13] reduction in plasma glucagon concentrations,[14] delayed gastric emptying,[15] and caused appetite suppression.[17] Appetite suppression and delayed gastric emptying are thought to be responsible for the weight-lowering effects of GLP-1.[18] The beneficial effect on body weight, cardioprotective effects, and blood glucose lowering effect make Saxenda a suitable agent for short- and long-term management of obesity.[19,20] Therefore, in the case report below, I will illustrate the benefits of using Saxenda as a treatment adjunct for a case of obesity associated with T2DM.

CASE REPORT

This case report concerns a 52-year-old man with a weight of 127.5 kg and height of 1.80 m who was recently diagnosed as having T2DM. There is a family history of obesity and T2DM, with both father and a brother suffering from the diseases. The patient was asymptomatic on presentation, with no signs of recent weight loss, polydipsia, polyuria or infections. He came to the office for a medical assessment. The BMI was 39.4 kg/m^2, above the level of 30.0 kg/m^2 which defines obesity. Similarly, his waist circumference (WC) was 114 cm, above the obesity threshold of 102 cm. At this level, the patient is at increased risk of developing obesity-associated metabolic complications. His fasting blood glucose was 8.2 mmol/l (n = 3.3–5.8 mmol/L). Hemoglobin A1C (HbA1c) was 7.7%, above the accepted level of 7%. Blood pressure (145/90 mmHg; n = 130/80 for a T2DM patient), triglycerides were elevated (2.6 mmol/l; n $\leq$ 1.7 mmol/L) and cholesterol (6.0 mmol/l; $n \leq 5.2$ mmol/L) while high-density lipoprotein (0.8 mmol/l; $n \geq 0.9$ mmol/L) was moderately decreased. There was a trace of protein and glucose in the urine, and the patient was receiving no medication at this time.

How we should educate this patient as the first step?

a. Assessing how ready the patient was about changing lifestyle habits.
b. A realistic weight loss goal is to maintain a reduction of 5–10% of initial body weight.
c. Reduce body weight and improve glycemic control.
d. Adequate surveillance.
e. All of the above are true.

Response E

Assessing how ready the patient was about changing lifestyle habits

It is important to begin the assessment of this patient by assessing how ready the patient is about making lifestyle changes. We did this using a readiness to change scale and using motivational interviewing. This is largely explained in many publications from the above author.[10,21-23] This includes assessing at where the patient was at the time of the first visit by establishing how he gained his weight and over what period of time. Then, we emphasized on the importance of changing lifestyles to help the patient losing weight and improve his glycemic control.

Let's assume that the patient is ready to make lifestyle changes. Then, I asked him to complete a food diary and assess his level of physical activity. I also assessed his stress level and social support. Then, I prescribed lifestyle modifications as the first step intervention. To increase adherence for physical activity, I recommended gentle exercise such as asking him to walk for a few minutes a day and gradually building up to 30 min a day. This helps to improve the patient's feelings about themselves. It is important to recognize that modest lifestyle changes can have an important impact on patient's well-being. This is illustrated in a recent report from Dr. Plourde.[23] Then, I suggest that even small calorie and physical exercises energy deficits are important, rather than trying to reach an "ideal" body weight right away? I also worked on stress management which is also an important component of success in weight loss interventions. We all recognize the need to recognize the stage of change in each patient. However, many patients do not seem to be ready to change for various reasons including

the socioeconomic context, race, ethnicity, false believes, and others and so for them trying to reduce weight is difficult, and for them, we need to be very progressive in our lifestyles interventions[10,22,23] You educate the patient that by doing small change at a time might start making a difference, which you then reinforce as success doing small changes bring motivation for further changes. It is not only easy but also it can be done. For more information on this approach, please consult the works of Dr. Plourde.[10,22,23]

A realistic weight loss goal is to maintain a reduction of 5–10% of initial body weight

Once the patient has accepted to make lifestyle changes, we should then propose a realistic weight loss goal such as to maintain at long-term a reduction of 5%–10% of their initial body weight.[10] Decreasing WC is particularly important as a reduction of 10 % in WC will generally result in around a 25% reduction in visceral fat, which is the most important factor for reducing CV risk.[10] It is interesting to explain that, if the patient was able to maintain a 5%–10% reduction of his initial body weight at long-term, the following improvements could also be anticipated: A blood pressure reduction of 10 mmHg, a 30% reduction in fasting blood glucose, a 15% reduction in HbA1c, and a 10% reduction in cholesterol as well as improve health benefits.[10,22,23]

Reduce body weight and improve glycemic control

The aims of management of our patient should be to reduce his body weight and improve glycemic control. Reducing WC, an index of central obesity, is particularly important.[10] The aim of long-term glycemic control in asymptomatic patient is the prevention of T2DM and its associated complications. In this particular patient, I would be looking at a caloric deficit of around 500 calories a day: 250 calories per day from regular physical exercise and 250/day from modest dietary changes.[10] The objective is to lose about 1 lb per week to achieve a 5%–10% weight loss and then to maintain it.[10,22,23]

Adequate follow-up

Ideally, the patient will initially be seen once a week by a member of the team. It is generally accepted that a multidisciplinary approach for the management of obesity works the best.[10,22-24] At the beginning, we see the patient once a week for the 1st weeks, and then, the patient is seen once every 2 weeks thereafter, and eventually, the visit was scheduled with the patients into monthly group meetings. That is the ideal situation, but one should realize that many primary care physicians (PCPs) have to limit their intervention because of their busy regular clinical practice.[25] There are excellent data showing that PCPs seeing their patients for 10 ± 15 min every month help to accomplish patient's weight loss goal.[25] Therefore, if PCPs can help patients with a lifestyle approach and good results can be achieved, even if patients cannot be seen less often than in the ideal situation.[10,22-25]

The patient was then treated with an energy deficit diet and increase regular physical activity for 3 months as this is the first step recommended before introducing pharmacotherapy in T2DM patient.[10,26] Actually, even with all the education provided and support the patient loss only a minimal amount of weight (5 kg) during that period of 3 months and this was explained by a lack of motivation, lack of time and others in the following of the lifestyle interventions discussed above. Nevertheless, the global metabolic profile has changed in response to lifestyle changes but not to an appreciable extent; there was a modest 0.9 mmol/l decrease in fasting glucose level. All other metabolic parameters remained unchanged or minimally changed. It was, therefore, decided to try to initiate GLUCOPHAGE® (metformin) therapy, 500 mg BID. One of the reasons for choosing metformin was because of its neutral effect on body weight.[26] It was also decided to put the patient on weight loss pharmacotherapy to help him increase his weight loss. Among the following what should be the best pharmaceutical aid for our patient that failed to reach his objectives by lifestyles interventions only?

a. Orlistat (Xenical)
b. Sibutramine (Meridia)
c. Lorcaserin (Belviq/Belviq XR)
d. Naltrexone/bupropion (Contrave)
e. Phentermine and Topiramate extended-release (long acting) capsules (Qsymia)
f. Liraglutide (Saxenda).

Response F
Orlistat (Xenical)

Orlistat is a gastrointestinal lipase inhibitor, when used in conjunction with changing lifestyle habits, is indicated for obesity management including weight loss and reducing the risk of weight regain in obese patients after prior weight loss.[27] This agent reduces the absorption of ingested fat by about 30%. The indications for the use of orlistat apply to obese patients with a BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 in the presence of other risk factors such as hypertension, T2DM, dyslipidemia, and excess visceral fat.[27] The 1-year study of Hollander *et al*., published in Diabetes Care, found a statistically significant mean weight loss of 6.2% in patients with T2DM.[28] There was also an accompanying mean reduction in WC, indicating a reduction in visceral fat. This is known to lead to a reduction in comorbid factors such as insulin resistance, lipid abnormalities, hypertension, and others.[28] The weight loss induced by orlistat improves glycemic control in T2DM patients and reduces the risk of developing T2DM in obese patients. Orlistat can be used in combination with anti-diabetic agents (sulfonylureas, metformin, and insulin) to improve blood glucose control in overweight or obese T2DM patients who are inadequately

controlled on diet, exercise, and one or more of a sulfonylurea, metformin, or insulin.[27] On the other hand, in controlled obesity management clinical trials of 1- and 2-year duration, 8.8% of patients treated with orlistat discontinued treatment due to adverse events, compared to 5.0% of placebo-treated patients.[27] Similarly, in the 4-year XENDOS clinical trial, 8.0% and 4.0% of patients treated with Orlistat and placebo, respectively, discontinued treatment due to adverse events.[29] For Orlistat, the most common adverse events resulting in discontinuation of treatment were gastrointestinal.[29] Since XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene, patients should be counseled to take multivitamin containing fat-soluble vitamins to ensure adequate nutrition. Due to adverse event associated with the use of Orlistat such as oily spotting, flatus and discharge, fecal urgency, fatty/oil stool, and other gastrointestinal events, A is not the best choice.

Sibutramine (MERIDIA)

Sibutramine, a selective serotonin and norepinephrine reuptake inhibitor, was approved by the FDA regulators in 1997. Clinical trials demonstrated that sibutramine-induced weight loss of about 3.62–5.29 kg improved lipid profile and glucose tolerance; however, it also increased blood pressure and pulse rate, which are important side effects.[30] The Sibutramine CV Outcomes Trial, a randomized CV outcomes study in patients with CV disease, T2DM, or both, found that sibutramine caused a greater rate of CV events and stroke.[31] Therefore, the benefit-risk profile of sibutramine was considered unfavorable by the FDA and Health Canada given the uncertainties surrounding the CV implications and the risk of stroke associated with sibutramine; therefore, this drug was voluntarily withdrawn from the Canadian and US market in 2010. Therefore, B is not an appropriate choice.

Lorcaserin hydrochloride (BELVIQ/BELVIQ XR)

Lorcaserin hydrochloride is a weight loss medication approved by the FDA, but it has not been marketed in Canada.[32] BELVIQ/BELVIQ XR is a serotonin 2C receptor agonist indicated as a pharmaceutical aid to a reduced-calorie diet and increased physical activity for chronic weight management of adult patients with an initial BMI of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition such as hypertension, dyslipidemia and T2DM. In clinical trials, researchers studied around 8000 overweight and obese patients. The average amount of weight loss among those tested subjects was 3–3.7% of their initial body weight.[32] This medication should be discontinued if 5% weight loss is not achieved by 3 months as in our patient. The most common adverse reactions (<5%) in non-diabetic patients are headache, dizziness, fatigue, nausea, dry mouth, and constipation and, in diabetic patients, are hypoglycemia, headache, back pain, cough, and fatigue. Since Belviq/Belviq XR are serotonin receptors, one should pay attention to the following serious ADRs such as serotonin syndrome or neuroleptic malignant syndrome (NMS)-like Reactions and others. The safety of coadministration with other serotonergic or antidopaminergic agents has not been established. Moreover, the effect of BELVIQ/BELVIQ XR on CV morbidity and mortality has not been established. For these reasons, C is not the best option.

Naltrexone/bupropion (Contrave)

Naltrexone hydrochloride 8 mg and bupropion hydrochloride 90 mg combined together have been marketed under the name of Contrave. Contrave is a sustained-release formulation of naltrexone that has been combined with a sustained-release formulation of bupropion. It is indicated for weight loss in people who have been diagnosed with an initial BMI of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as controlled hypertension, T2DM, or dyslipidemia. Contrave has recently been approved by Health Canada and is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults.[33] According to clinical studies, CONTRAVE can help to promote weight loss, but the numbers are not impressive. In a study of patients without diabetes, only 42% of patients lost at least 5% of their body weight after a year. That means that most people taking Contrave did not meet the weight loss goal.[33] In addition, the effect of Contrave on CV morbidity and mortality has not been established, but it is known that it can increase blood pressure and heart rate. Contrave should not be given to patients with uncontrolled hypertension and should be used with caution in patients with controlled hypertension. Contrave contains bupropion which as the potential association with behavioral and emotional changes, including self-harm, and has the potential for seizure.[33] Therefore, Contrave is not the best option.

Phentermine and topiramate extended-release (long-acting) capsules (Qsymia)

On July 17, 2012, the FDA approved a tablet combining phentermine plus extended-release topiramate (Qsymia) for weight loss. Phentermine has been used for weight loss, and topiramate is an antiepileptic agent that has been commonly associated with weight loss as a side effect. Phentermine and topiramate extended-release (long-acting) capsules are used to help adults who are obese or who are overweight and have weight-related medical problems to lose weight and to keep from gaining back that weight.[34] Phentermine and topiramate extended-release capsules must be used along with a reduced calorie diet and a physical exercise program. Phentermine has been used for weight loss and is in a class of medications called anorectics that works by decreasing appetite. This combination works synergistically to cause weight loss at lower doses compared with the individual products used alone, thereby reducing adverse effects. In clinical trials, patients who took a lower dose of the weight loss medication (3.75 mg

phentermine/23 mg topiramate) lost an average of 6.7% of their weight.[34] The types of adverse effects demonstrated in clinical trials were similar to those of the single products. The most notable adverse reactions of the individual products include CV and cognitive dysfunction. There were no serious CV events during the trials, and discontinuation of treatment attributable to cognitive dysfunction rarely occurred.[34] Due to the risk of teratogenicity, the patient, prescriber, and certified pharmacy must all comply with the FDA-mandated risk evaluation and mitigation strategies (REMS) program for this medication. The REMS consists of informing the prescribers and females of reproductive potential about the increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy; the importance of pregnancy prevention for females of reproductive potential receiving Qsymia; and the need to discontinue Qsymia immediately if pregnancy occurs. Due to the associated risk for CV events, in particular with phentermine, Qsymia is not the best option.

Liraglutide (Saxenda)

Liraglutide is a GLP-1 receptor agonist, marketed as Saxenda® and Victoza® (12, 35). Saxenda (liraglutide; 3.0 mg) is approved for weight loss in addition to diet and regular physical activity for patients with a BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 plus at least one weight-related illness such as hypertension, dyslipidemia, or T2DM as in our patient.[12] This drug has been studied in a number of large clinical trials, and meta-analysis has demonstrated that Saxenda was able to produce an average weight reduction of 6.3–8.0 kg over and above that achieved with placebo (lifestyle changes only) at 1 year of therapy.[35,36] Saxenda has shown encouraging results for weight loss in obese patients in multiple phase III clinical trials.[37-42] A recent meta-analysis comparing the effectiveness of the above medications demonstrated that Saxenda was one of the medications associated with the highest odds of achieving at least 5% weight loss as compared with placebo,[43] lorcaserin or orlistat, similar odds as compared with naltrexone/bupropion, and slightly lower odds as compared with phentermine/topiramate.[43]

Saxenda may be a particularly effective choice among obese patients with T2DM as in our patient and can be considered for those at high risk for CV disease given a beneficial signal in CV outcomes seen in the 1.8 mg formulation.[43] However, the effects of the 3.0 mg formulation on CV morbidity and mortality have not been established.[43]

The most common adverse event associated with Saxenda with prevalence >5% is nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, dyspepsia, fatigue, dizziness, and abdominal pain which usually goes away with time.[12] Saxenda should be used with caution in patients with impaired kidney or liver function.[12] Patients starting treatment with Saxenda should be cautioned about the risks of acute pancreatitis, acute gallbladder disease, serious hypoglycemia, heart rate increase, and hypersensitivity reactions that are rare adverse reactions associated with Saxenda.[12]

Saxenda is labeled for use with metformin; the dose of Saxenda must be titrated up on a weekly basis starting from 0.6 mg/day in weekly intervals of 0.6 mg, taking 5 weeks to achieve the maintenance dose of 3.0 mg daily. Finally, Saxenda combined with diet and regular physical activity was able to maintain the weight loss over 56 weeks suggesting a role for Saxenda on weight loss maintenance at long term.[41] Improvements in some CV disease-risk factors were also observed.[41] Therefore, E is the best choice.

CONCLUSION

In our patient, the addition of Saxenda 3.0 mg/day to the above lifestyle interventions resulted in an additional 9 kg weight loss, i.e., a total loss of more than 10% (10.9%) of his initial body weight of 127.5 kg. With this treatment, we also noted a great improvement of his T2DM to the point that we were able to discontinue metformin. The addition of Saxenda has also permitted to normalize his metabolic profile. Considering that our patient still has a BMI of 35.0 kg/m^2, the following objective is to continue losing weight and maintaining at long term his weight loss as well as his improved metabolic profile with lifestyle changes combined with Saxenda. The most common adverse effects observed with Saxenda in our patient were from the gastrointestinal system mostly nausea and occurred early (few initial weeks) in his treatment course and were easily manageable. Interestingly, no hypoglycemic episodes have occurred during his treatment.

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