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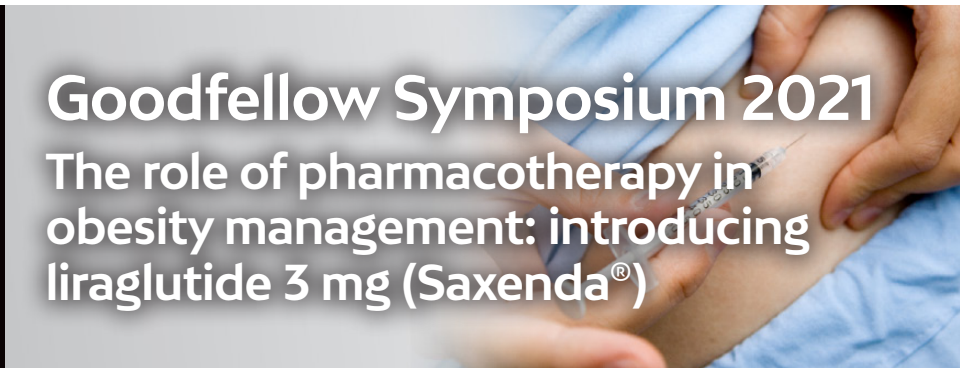
SPEAKER SERIES

Goodfellow Symposium 2021

The role of pharmacotherapy in obesity management: introducing liraglutide 3 mg (Saxenda®)



Making Education Easy 2021

About the speakers

Michael Cowley

Professor Michael Cowley is Head of the Department of Physiology at Monash University in Melbourne. Michael is a physiologist widely recognised for his research into the causes of obesity and obesity-related diseases such as diabetes and has published more than 120 papers and chapters and is the inventor of 85 patents.

Sean Wharton

Dr Sean Wharton obtained his doctorates in Pharmacy and Medicine from the University of Toronto. Sean is the medical director of a community-based internal medicine weight management clinic and he also works as an internal medicine specialist. His research focuses on bariatric medicine and type 2 diabetes and he has published or contributed to many peer-reviewed articles and is the lead author on the 2020 Canadian Obesity Management guidelines.

Georgia Rigas

Dr Georgia Rigas is a Sydney-based GP and a Senior Bariatric Medical Practitioner involved in a number of clinical research projects. She was the founding Chair of the Obesity Management Specific Interest Network within the RACGP and serves on a number of scientific medical advisory committees in Australia and abroad.

RESEARCH REVIEW™
Making Education Easy — Since 2006

This publication summarises a session from the virtual 2021 Goodfellow Symposium. Speakers from Canada and Australia discussed the prescription weight loss medication, liraglutide 3mg. Key topics included bodyweight regulation and the central effects of liraglutide 3mg in energy homeostasis and appetite regulation, as well as efficacy and safety in different populations, concluding with a case study. The Goodfellow Symposium is a primary care symposium designed for GPs, urgent care physicians, nurses, nurse practitioners and registrars. This Goodfellow session and write up was supported by Novo Nordisk.

BODY WEIGHT REGULATION AND CENTRAL EFFECTS OF LIRAGLUTIDE 3 MG IN ENERGY HOMEOSTASIS: APPETITE REGULATION

Professor Michael Cowley

Periods of weight gain following weight management interventions are almost inevitable for some patients. Approximately 80% of people who lose weight with lifestyle interventions regain that weight over the next two to five years.[1] Weight gain is a physiological response to weight loss and should not be regarded as a failure as this stigma can be harmful to patients.

The physiological drivers of weight gain following weight loss are:

1. A desire to increase energy intake
2. An unconscious reduction in energy expenditure

The increased hunger and desire to eat following weight loss is driven by hormonal changes including the decreased secretion of GLP-1, CCK and PYY, the increased secretion of ghrelin, and a decrease in leptin production due to a decrease in fat mass.[2,3]

The hormonal changes that occur following weight loss also cause metabolic changes via a reduction in sympathetic nervous system activity.[4] This causes the body to become more energy efficient, thereby creating an 'energy gap' due to a reduction in energy expenditure.[4] For example, a 10% reduction in body weight is followed by an approximate 300 kilocalorie per day decrease in total energy expenditure, despite activity levels remaining relatively constant.[5]

The physiological adaptions to weight loss are the main reasons why diets generally fail and why patients need additional assistance to lose weight.

The role of endogenous glucagon-like peptide-1 (GLP-1)

GLP-1 is a member of the incretin family and is secreted by L-cells in the gut and in the nucleus tractus solitarius in the brain. One of the reasons GLP-1 is involved in diabetes treatment is because it stimulates insulin secretion. The half-life of endogenous GLP-1 is approximately two minutes because it is degraded by the enzyme DPP-4 and therefore it does not have a significant role in weight loss interventions.[6] GLP-1 is released following food intake throughout the day.[7] Receptors for GLP-1 are widely expressed, particularly in the brain and pancreas.[8]

The post-prandial release of GLP-1 activates brain regions that are implicated in the regulation of satiety and food intake.[9] The peak postprandial increases in GLP-1 concentrations are correlated with increases in regional cerebral blood flow in the left dorsolateral prefrontal cortex and the hypothalamus.[9]

Abbreviations used in this review

BMI = body mass index
BP = blood pressure
CCK = cholecystokinin
DHEAS = dehydroepiandrosterone
DPP-4 = dipeptidyl peptidase 4
GERD = gastroesophageal reflux disease
GLP-1 = glucagon-like peptide-1
Hb = haemoglobin
LOCF = last observation carried forward
MACE = major adverse cardiovascular events
MTC = medullary thyroid cancer
PCOS = polycystic ovary syndrome
PTH = parathyroid hormone
PYY = peptide YY
ULN = upper limit of normal
WC = waist circumference

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Liraglutide 3 mg (Saxenda®)

Liraglutide has 97% amino acid homology with endogenous human GLP-1, is slowly absorbed following subcutaneous administration and is resistant to DPP-4 degradation.[10] Its plasma half-life of 12-13 hours makes liraglutide 3 mg suitable for once-daily therapeutic use.[10] Labelled liraglutide administered in the periphery distributes to the same areas in the hypothalamus and brainstem of mice that GLP-1 activates in human brains.[11]

Liraglutide (3 mg, daily) modifies several dimensions of human appetite. Up to five hours after eating, patients taking liraglutide report sensations of satiety and fullness to be increased, while hunger and intention to eat are decreased over the same period (**Figure 1**).[12] Liraglutide therefore reduces energy intake, but it does not influence energy expenditure.[12] Liraglutide is unlikely to be associated with adverse cardiovascular effects because it does not modify sympathetic nervous system activity.

Mild and transient nausea is frequently reported by patients taking GLP-1 analogs. The weight loss associated with liraglutide 3 mg is not, however, attributable to nausea or vomiting.[13]

PRACTICE POINTS SUMMARY:

- Weight gain is a natural physiological response to weight loss
- Weight gain following a weight loss intervention is not a patient failure and this harmful stigma should be avoided

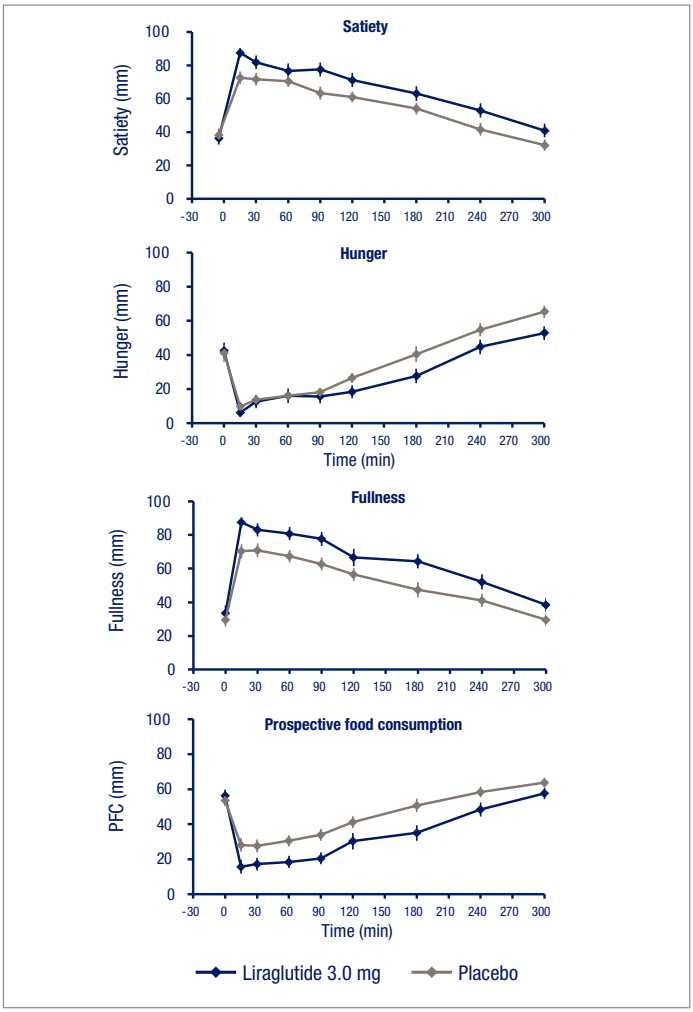

Figure 1: Appetite ratings as assessed by visual analog scales following breakfast, adapted from van Can *et al.* (2014)[12]

EFFICACY AND SAFETY OF LIRAGLUTIDE 3 MG IN DIFFERENT POPULATIONS: SCALE™ STUDY OVERVIEW

Dr Sean Wharton

Liraglutide 3 mg was approved in the United States and elsewhere on the basis of four key studies referred to as the Satiety and Clinical Adiposity — Liraglutide Evidence in nondiabetic and diabetic individuals (SCALE) global clinical trials.[13–17]

SCALE Obesity and Pre-diabetes

The SCALE Obesity and Pre-diabetes study was the largest SCALE trial,[13] with patients randomised in a 2:1 ratio to the liraglutide 3 mg or placebo arm of the trial. The dose of liraglutide was titrated upwards over four weeks and weight change and other metabolic parameters were examined. Both trial arms received counselling on lifestyle interventions.

After 56 weeks, patients receiving liraglutide 3 mg reduced their mean bodyweight by -8.0% (-8.4kg, **Figure 2**), patients in the placebo group lost -2.6% (-2.8kg, $P < 0.001$).[13] Patients who are early responders , i.e. ≥ 5% reduction in bodyweight after 12 weeks, may achieve a double-digit reduction in body weight (-11.2% mean).[18]

SCALE Maintenance

The SCALE Maintenance trial was designed to mirror clinical practice. This study involved a 12-week period where diet and exercise alone were associated with an approximate -6% reduction in bodyweight (**Figure 3**); patients who did not achieve a -5% reduction were not eligible for randomisation.[17]

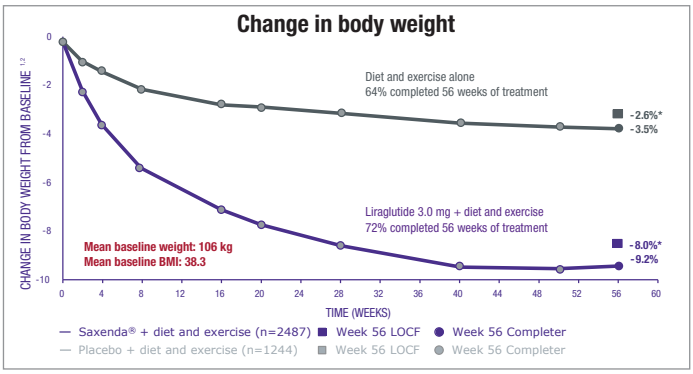

Figure 2: Percentage change in mean body weight for patients receiving 3 mg liraglutide, daily, and placebo, adapted from Pi-Sunyer *et al.* (2015)[13], P<0.001

At the 12-week point, liraglutide 3 mg, daily, was introduced to the treatment arm and patients taking liraglutide 3 mg lost an additional -6.2% after 56 weeks of treatment ($P < 0.0001$).[17] Dr Wharton noted that following withdrawal of liraglutide 3 mg, patients increased their bodyweight which is consistent with liraglutide 3 mg being an effective weight loss medicine.

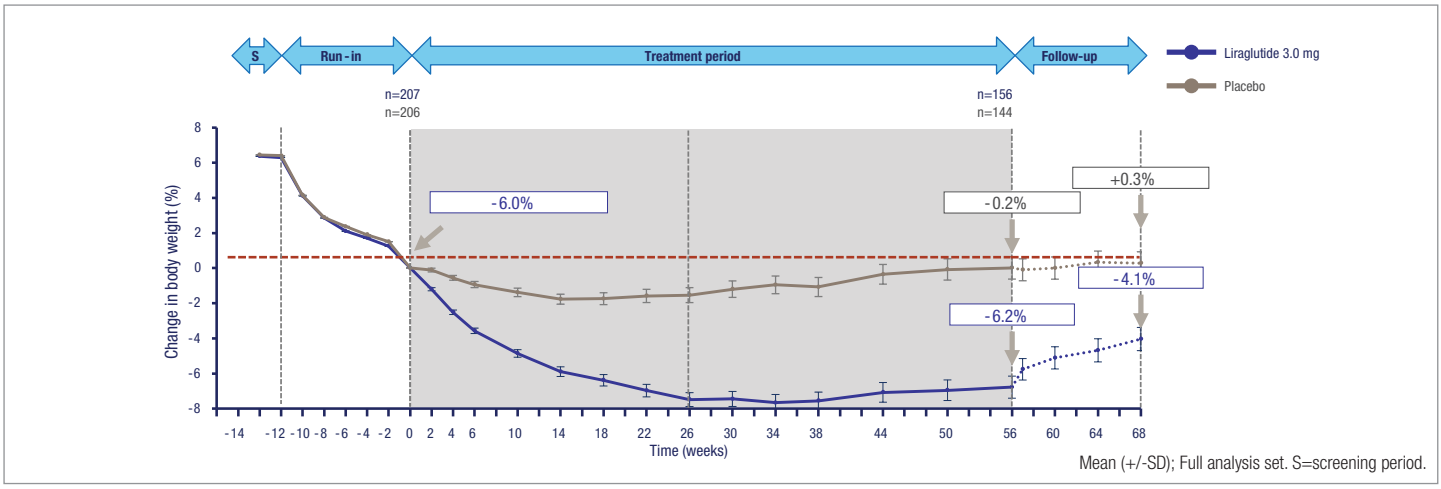

Figure 3: Percentage change in mean body weight for patients receiving 3 mg liraglutide, daily, versus placebo, adapted from Wadden *et al.* (2013)[17]

In addition to weight loss, liraglutide 3 mg, daily, is associated with:

- Lower blood glucose levels and less risk of developing type 2 diabetes.[13,16,18]
- Decreased blood pressure and lipids.[13,16,18]
- Reduced severity of obstructive sleep apnoea.[14,18]
- Improvements in health-related QoL.[13,16,18]

Dr Wharton stressed that the QoL improvements associated with liraglutide 3 mg are one of the most important benefits of treatment.

The safety of liraglutide

The obesity and pre-diabetes SCALE trial was extended to three years and a -7.1% reduction in body weight occurred in the 53% of patients who completed treatment, compared to a -2.7% reduction in the placebo arm.[16] Dr Wharton pointed out that this suggests that liraglutide 3 mg helps to suppress the physiological adaptions to weight loss for at least three years. Gastrointestinal adverse effects comprised 93% of adverse events reported by patients (**Table 1**).

Table 1: Selected adverse events associated with liraglutide 3 mg, daily, and placebo[16]

Adverse effect	Liraglutide group - event rate per 100 years of observation	Placebo group – event rate per 100 years of observation
Nausea	29.9	11.3
Diarrhoea	19.0	9.9
Vomiting	14.7	3.6
Headache	13.3	14.9
Constipation	13.0	6.8
Gallbladder-related events	2.9	1.2
Pancreatitis	0.3	0.1
MACE	0.19	0.2
MTC or confirmed C-cell hyperplasia	0	0
Neuropsychiatric events	Similar in both groups	

Nausea and vomiting occurred primarily within the first four to eight weeks of liraglutide treatment.[13] Dr Wharton recommends that patients be advised of the potential risk of nausea, vomiting and dehydration associated with liraglutide and the dose reduced if necessary.

Real-world clinical evidence

A real-world clinical study was conducted at the Wharton Medical Clinic in Ontario. Data was included for all weight-management patients (*n*=849) who received a liraglutide 3 mg prescription between September 2015 and September 2016.[19] Of the 311 patients who met all inclusion criteria and none of exclusion criteria, 210 patients (67%) persisted with liraglutide 3 mg for at least four months and 167 patients (54%) persisted for at least six months. Dr Wharton noted that this compares to approximately 20% of patients who typically persist with weight loss treatment in a normal clinical population. The mean weight loss for patients who persisted with liraglutide 3 mg treatment is shown in **Figure 4**. At six months follow-up, 63.4% of patients had lost ≥ 5% of bodyweight and 35.2% of patients had lost > 10% of bodyweight.[19]

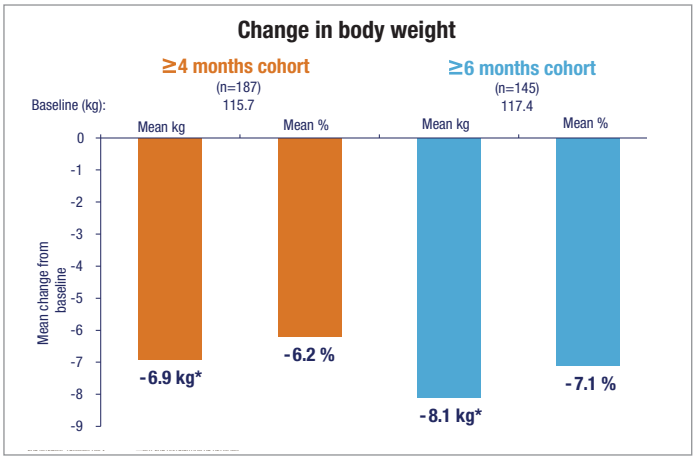

Figure 4: Mean weight loss kg and percentage in patients persistent with liraglutide 3 mg ≥ four months and ≥ six months, adapted from Wharton *et al.* (2019)[19] *Significant weight reduction (*P*<0.05)

Dr Wharton presented data showing adverse effects were self-reported by 66% of patients taking liraglutide 3 mg with the most common adverse effects being nausea (43.1%), constipation (15.4%), GERD (10%), fatigue (7.7%), injection site irritation (6.1%), diarrhoea (6.1%) and vomiting (5.8%).

Dr Wharton also reported that the most frequently reported features from patients taking ligraglutide 3 mg were decreased hunger (74.6%), improved portion control (61.1%), improved satiety (42.8%) and decreased cravings (27.7%).

PRACTICE POINTS SUMMARY:

- In a real-world setting, patients who persisted with liraglutide 3 mg treatment for at least six months lost approximately -8.0 kg of bodyweight
- Patients should be advised of the risk of nausea and vomiting in the first 4-8 weeks of treatment and the liraglutide 3 mg dose reduced if necessary
- Treatment with liraglutide 3 mg is associated with improvements in QoL and metabolic parameters in addition to weight loss.

THE ROLE OF LIRAGLUTIDE 3 mg IN MANAGING OBESITY

Dr Georgia Rigas

Dr Rigas introduced Nicole, a 36-year-old, nulliparous woman who underwent lapband surgery in 2010. Her heaviest ever weight as an adult was 132 kg and she reached a nadir weight of 79 kg with the lapband. Nicole works as a flight attendant and lives with her partner of 12 months. She is excited about the prospect of starting a family but is stressed about recent weight regain and concerned her periods have become irregular since the weight regain. Nicole reports feeling tired and as a result has found herself "snacking". She has also been subjected to workplace bullying with the stress causing her to seek calorie-dense "comfort" food. Nicole's lapband is optimally adjusted and her medical history and clinical features are shown in **Table 2**.

Table 2: Clinical findings for Nicole following examination

Examination:	**Medical history**:
Height = 167 cm Weight = 102 kg BMI = 36.6 kg/m^2 WC = 111.5 cm	Depression (well controlled) Anxiety (well controlled) PCOS
Medicines Escitalopram 20 mg/day	**Physical examination and blood work**: • BP = 130/70 mmHg • Hirsutism, acne and skin tags • Hb 118 g/L, iron 13 nmol/L, iron sat 19%, ferritin 15 µg/L • DHEAS 20 (ULN 13) other sex hormones normal • HbA_{1c} 5.3%, glucose 5.3 mmol/L and insulin 15.4 mU/L (ULN 10) • Vitamin D 50 nmol/L (ULN 375), corrected calcium normal, PTH 7.2 pmol/L (ULN 6.8)

Nicole's recent weight regain appears to have exacerbated her PCOS which had improved after the initial significant weight loss with the lapband. From her blood work iron deficiency anaemia is diagnosed; likely to be contributing to her fatigue. Her vitamin D levels are suboptimal for winter which is potentially a concern.

Treatment 1: Education

Dr Rigas's first course of action was to commend Nicole for seeking medical help and validate her concerns. Secondly, she provided education on the following points:

- Obesity is a chronic, progressive disease and periods of weight gain are normal and to be expected
- Stress and poor sleep can contribute towards inflammation and obesity
- Modest weight loss may help to improve PCOS and fertility

Dr Rigas provided encouragement by explaining that a 10% reduction in bodyweight is known to reduce androgens, increase insulin sensitivity and improve ovulation.

Treatment 2: Interventions

Dr Rigas introduced the following interventions:

- Treatment of iron deficiency anaemia and suboptimal vitamin D levels
- Discussing sleep hygiene and empowering Nicole to come up with workable solutions/strategies
- Asking Nicole to complete a food and mood diary before consulting with the dietitian.

Ongoing support from a multi-disciplinary team is important in the management of long-term conditions and Dr Rigas emphasised obesity is no different. A dietitian can encourage menu planning, food preparation, including batch cooking, provide suggestions for healthier food choices and educate patients about how nutritious habits improve health. Regular support from a psychologist may help Nicole develop stress management techniques to avoid eating as a maladaptive coping strategy.

Treatment 3: Treatment and follow-up

Dr Rigas discussed the therapeutic options available to Nicole, i.e. a very low energy diet and approved medicines to assist with weight loss and health improvement. Nicole preferred liraglutide 3 mg because she felt the mechanism of action "made sense" to her and she was encouraged by the health benefits demonstrated in the SCALE studies.

- Liraglutide 3 mg was prescribed as part of an overall approach that also included:
  - Regular structured and incidental physical activity
  - Healthier nutritional intake
  - Mindful eating

In Dr Rigas's clinic, the practice nurse shows patients how to use the Saxenda® injection pens, reiterates the dose escalation protocol and enrols patients in the SaxendaCare® patient support programme.

The dose escalation regimen

The liraglutide 3 mg dose escalation protocol is shown in **Figure 5**. If escalation to the next dose is not tolerated, Dr Rigas recommends the patient remain on the lower dose for an additional week. If the dose escalation is not tolerated for two consecutive weeks, consider discontinuing treatment.[18]

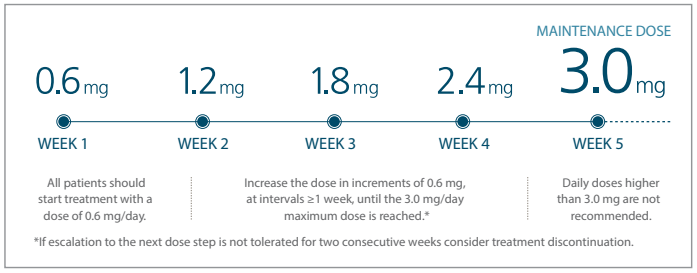

Figure 5: Dose escalation schedule for liraglutide 3 mg[18]

It is important that patients understand that the dose escalation protocol is designed to improve GI tolerability. Dr Rigas also provides an antiemetic prescription that can be filled if required. In Dr Rigas's experience, the nausea associated with liraglutide 3 mg is mild and transient and only a small minority of patients require an antiemetic, and for those that do it tends to be for one or two days after a dose escalation during the first four weeks. Dr Rigas also emphasised the importance of discussing weight loss expectations with patients as in her experience most health benefits start to occur once the therapeutic dose is achieved.

Once daily liraglutide 3 mg, can be taken at any time, independent of meals.[18] Some patients may initially be reluctant to self-administer a subcutaneous injection, however, in Dr Rigas's experience the majority are able to do so without issue if they are encouraged to "just give it a go". In some cases, the practice nurse helps the patient self-administer the first dose in the clinic to empower the patient.

Follow-up

Over the following months Nicole began menstruating regularly and she felt more self-confident. Her clinical progress and future management included:

- Baseline 102 kg with a BMI of 36.6 kg/m^2
- At week 16 lost 5 kg or -5% (BMI 34.2 kg/m^2)
- At week 36 lost 12 kg or -11.8% (BMI 32.2 kg/m^2)
- Washout period before trying to conceive; emphasis on the importance of pre-conception multivitamins and the need for all women with current or past obesity to take high dose folic acid (5 mg) before and early in pregnancy.
- Follow-up in 3 months; earlier if she becomes pregnant.

TAKE-HOME MESSAGES FROM THE SPEAKERS

The physiology of weight loss:

- Liraglutide 3 mg (Saxenda®) is a useful additional therapeutic weight loss intervention
- Liraglutide 3 mg works to decrease hunger and increase sensations of fullness and satiety
- Liraglutide 3 mg helps to cause weight loss and contributes to the maintenance of weight loss.

Evidence from clinical trials and real-world experience:

- In a real-world setting, patients who responded to liraglutide 3 mg and continued treatment for at least six months lost approximately -8.0 kg in body weight
- Mild and transient gastrointestinal symptoms are the most common adverse effects associated with liraglutide 3 mg
- Treatment with liraglutide 3 mg is also associated with improvements in glycaemic control, systolic blood pressure and patient QoL.

Practice points for primary care:

- Education about weight regain is an important aspect of weight management
- Liraglutide 3 mg, daily, may be prescribed as part of an overall weight management programme that also includes regular physical activity, healthy nutritional intake and mindful eating
- Discuss the possibility of GI adverse effects, the dose escalation protocol and the weight loss expectations of patients prior to prescribing liraglutide 3 mg.

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