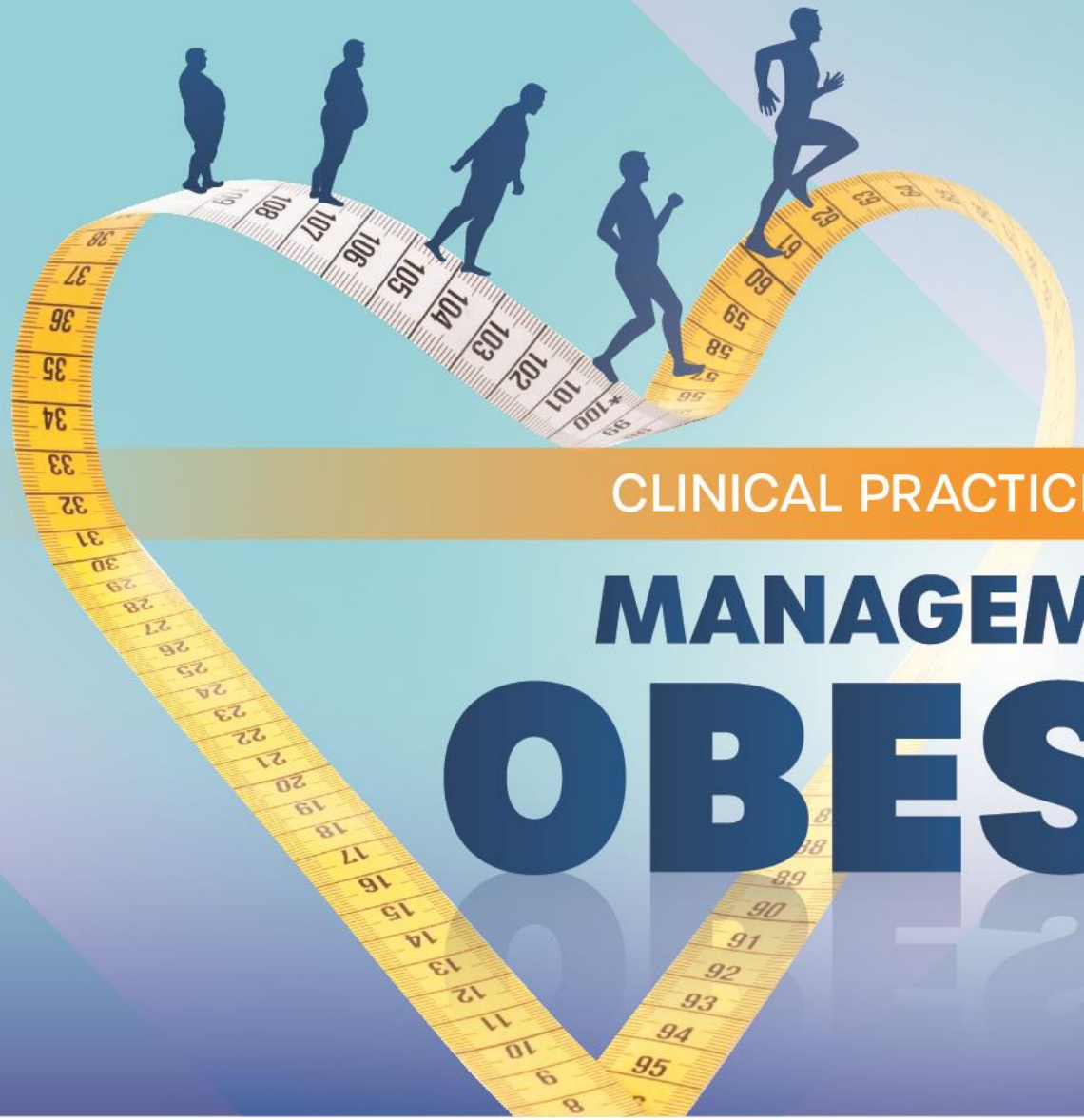


CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF OBESITY

2ND EDITION (2023)

Ministry of Health Malaysia

Malaysia Endocrine & Metabolic Society

Malaysian Association for the Study of Obesity

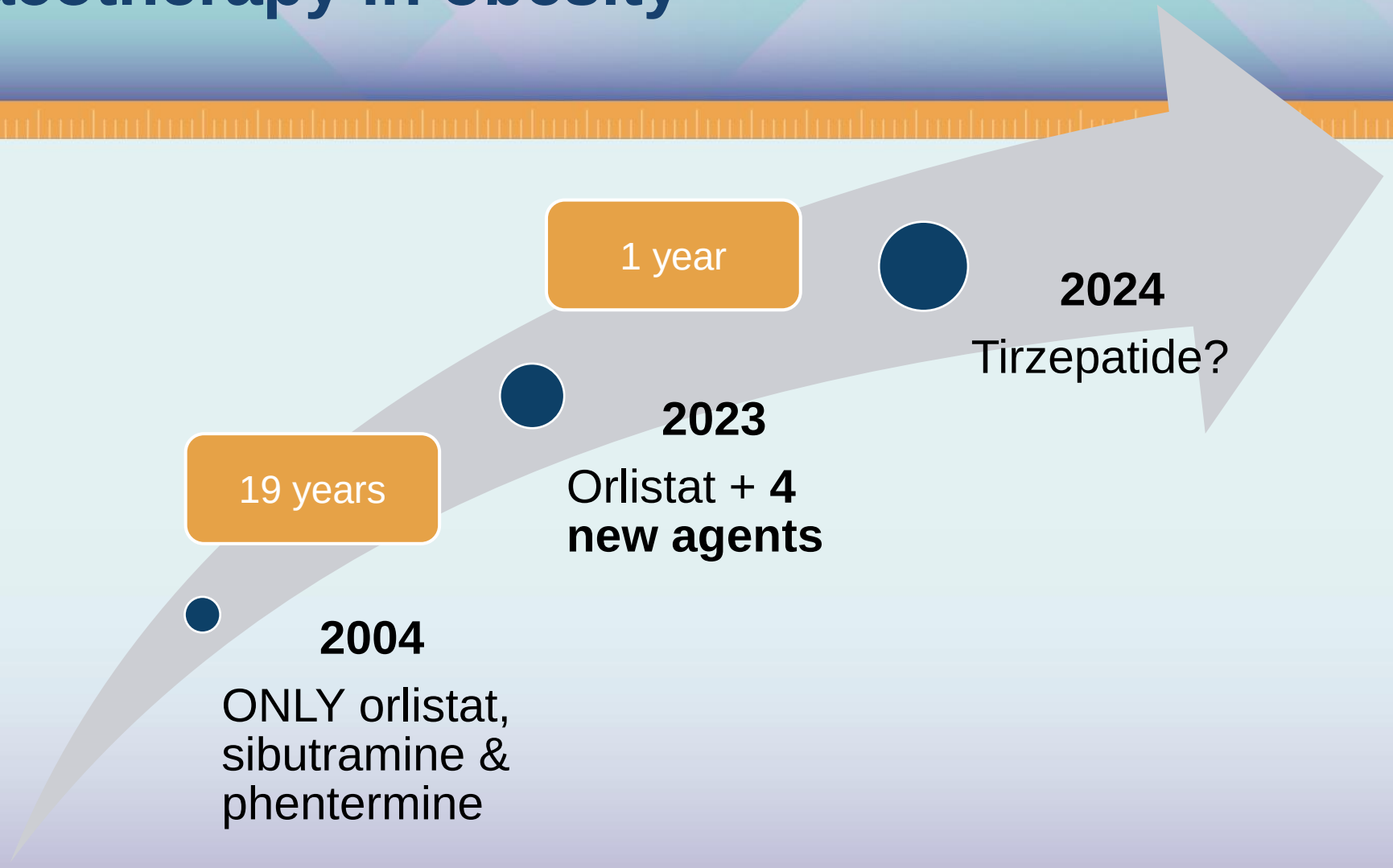
Malaysian Dietitians' Association

Family Medicine Specialists Association of Malaysia

Professor Dr Shireene Ratna Vethakkan

ANTI-OBESITY DRUGS

Pharmacotherapy in obesity



5 Recommendations

Recommendations 5

- Pharmacotherapy for obesity should be used only as an adjunct to diet, exercise and behavioural modification and not alone. **[Grade A]**
- Pharmacotherapy for obesity is indicated in patients with BMI ≥30 kg/m² without comorbidities and BMI ≥27 kg/m² with comorbidity. **[Grade A]**
- Pharmacotherapy that may be prescribed are:
  - Orlistat
  - Combination of phentermine and topiramate
  - Combination of naltrexone and bupropion
  - High dose liraglutide
  - High dose semaglutide

  [Grade A]
- Anti-obesity treatments should be used with medical supervision and careful monitoring. **[Grade B]**

Pharmacotherapy in obesity: Recommendation 1

WHEN?

- Achieving or maintaining weight loss **fails with lifestyle interventions**

WHY?

- To **aid compliance** with dietary restriction
- To **augment** diet-related weight loss
- To **achieve** weight maintenance after satisfactory weight loss

Pharmacotherapy in obesity: Recommendation 2

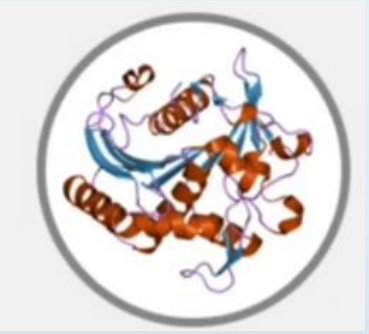
WHO?

Grade A
Level
1++

- Patients with BMI ≥30 kg/m^2 **without comorbidities**
- Patients with BMI ≥27 kg/m^2 **with comorbidities**

T2DM

Hypertension



Dyslipidemia

OSA

BMI, body mass index; OSA, obstructive sleep apnoea; T2DM, type 2 diabetes mellitus.

Reference: 1. Garvey WT, et al. Endocr Pract. Jul 2016;22 Suppl 3:1-203.

Pharmacotherapy in obesity: Recommendation 3

Grade A; Level 1++

As obesity is a chronic disease, long-term pharmacotherapy should be considered

	Weight loss from baseline in excess of placebo arm	% weight loss from baseline	Approved in Malaysia	Comments
Semaglutide 2.4 mg weekly(s/c)	12.7kg	14.9%		In obesity +T2DM, improves glycemia, cardiorenal outcomes & MAFLD
Phentermine/topiramate	8.8 kg	8-11%		Fixed-dose combination unavailable in Malaysia
Liraglutide 3mg daily(s/c)	5.24 kg	6-7%		In obesity +T2DM, improves glycemia, cardiorenal outcomes & MAFLD
Naltrexone/bupropion	4.95 kg	5-6%		
Orlistat	2.63kg	2.9-3.4%		

A note on phentermine

- Phentermine is **not US FDA approved for long-term treatment** due to its cardiovascular side effects.
- Should only be used for **≤3 months in a cyclical manner**

Pharmacotherapy in obesity: Recommendation 4

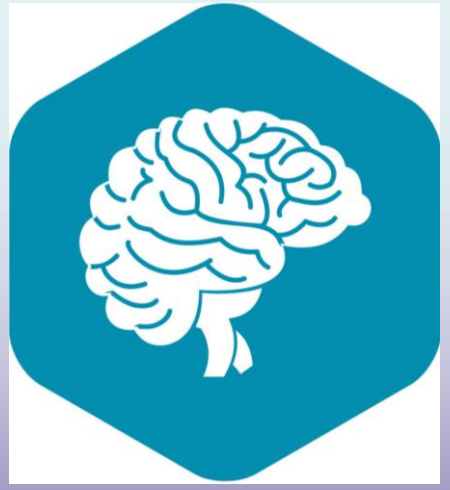
Grade B

Anti-obesity drugs should be administered with medical supervision and careful monitoring

Pharmacotherapy: Mechanisms of action

Gastrointestinal

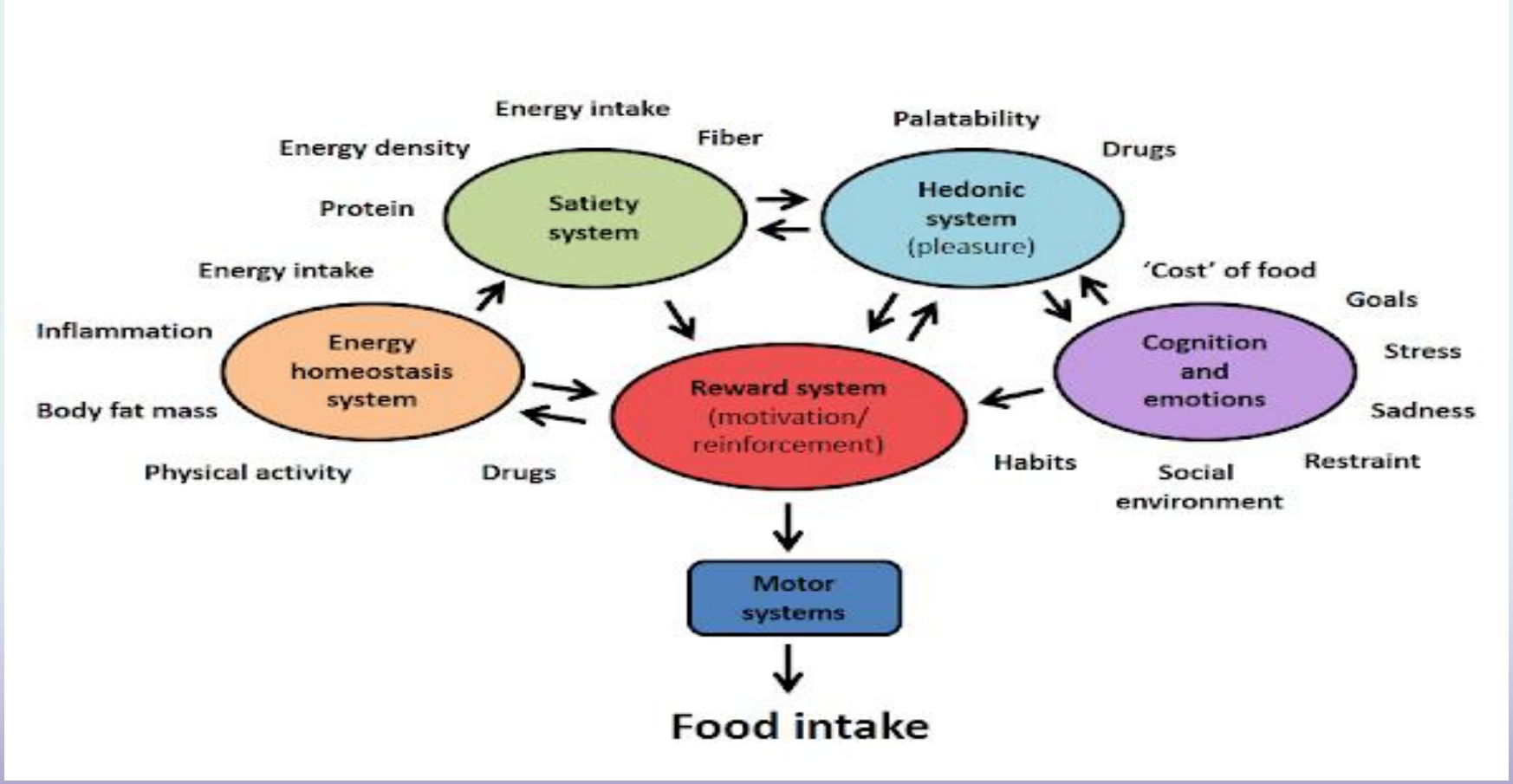
- Orlistat
- Lipase inhibitor



Central nervous system

- GLP1 receptor analogues
- Bupropion/naltrexone
- Phentermine/topiramte

Why do we eat? The big picture



Why do we eat? The molecular view (ROTI JALA PICTURE)

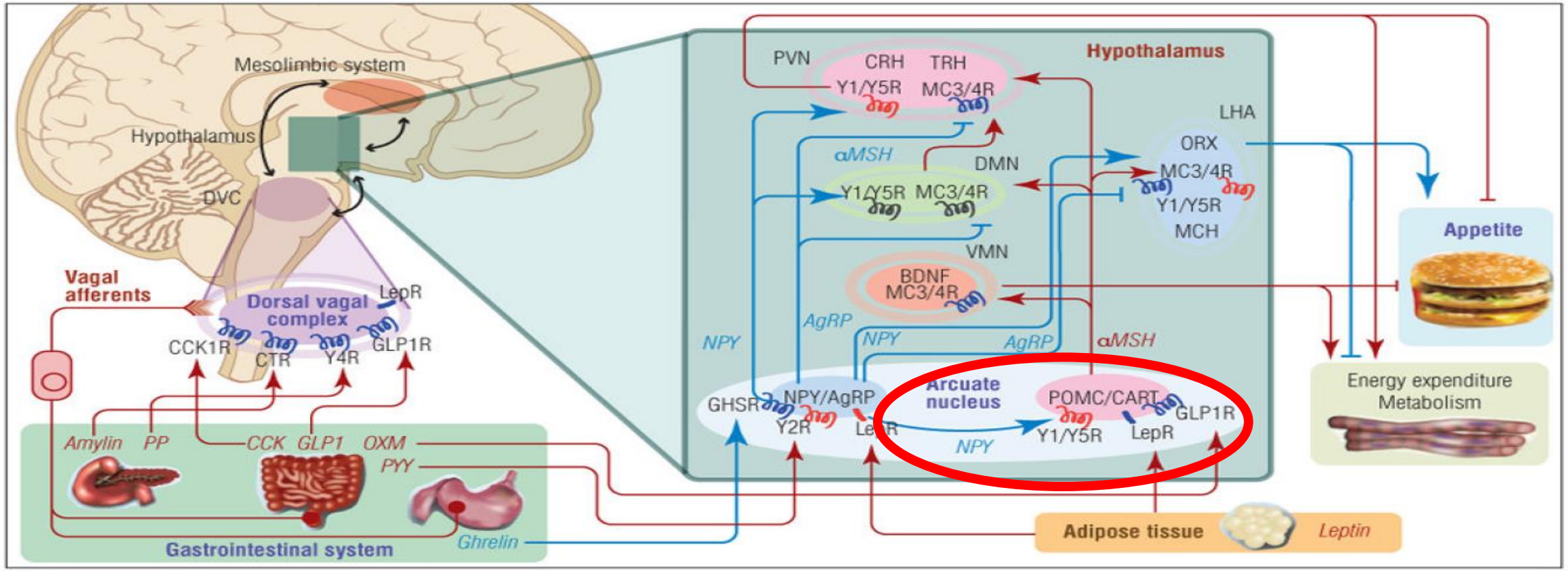
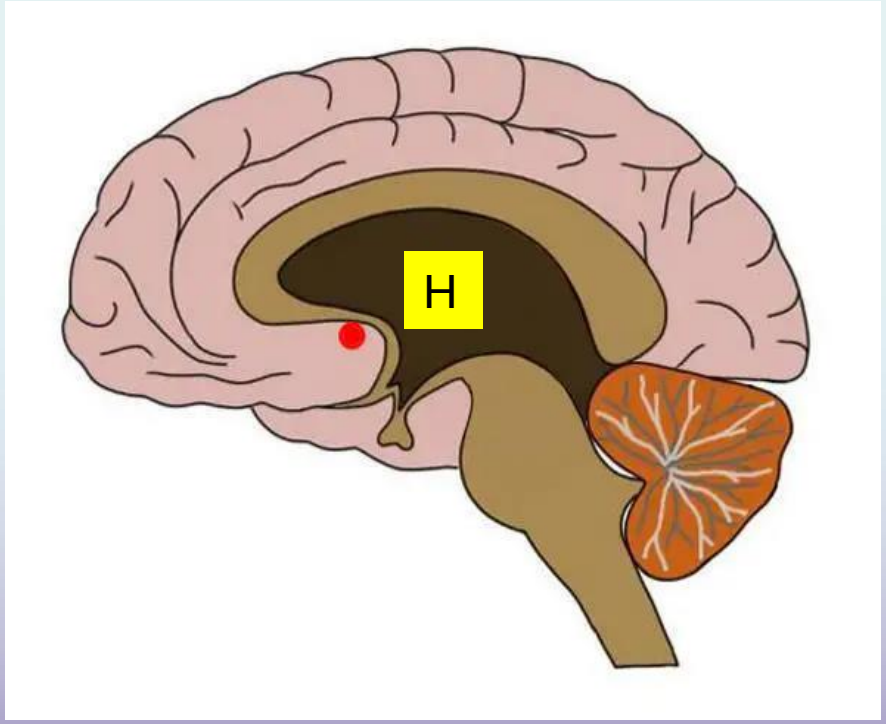
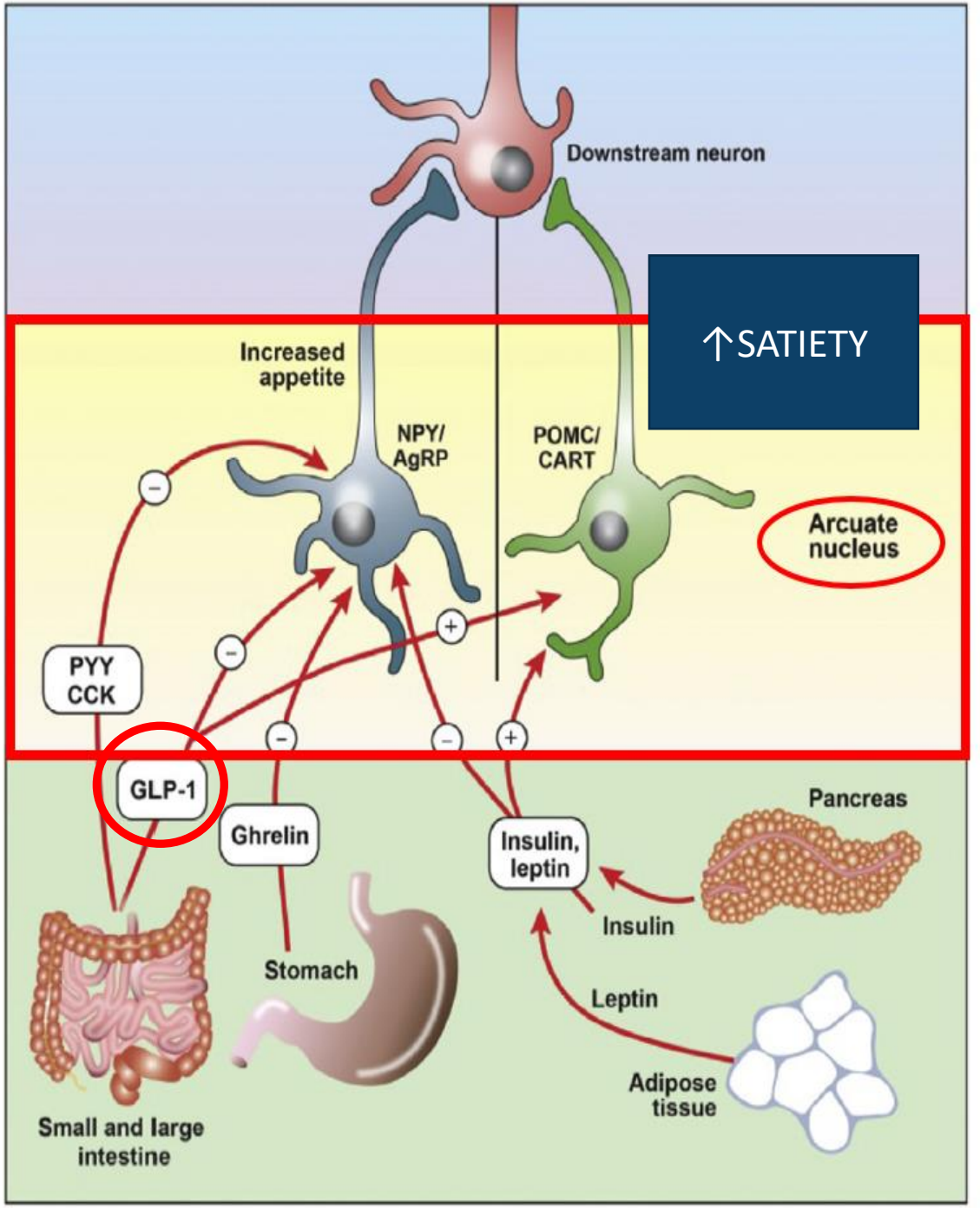


Figure 1. Central regulation of appetite and energy homoeostasis

Pharmacotherapy: Mechanism of action

GLP1-RA stimulates the POMC neurons
(Pro-Opio-Melano-Cortin)





Labradors are always hungry; they might have a POMC mutation!

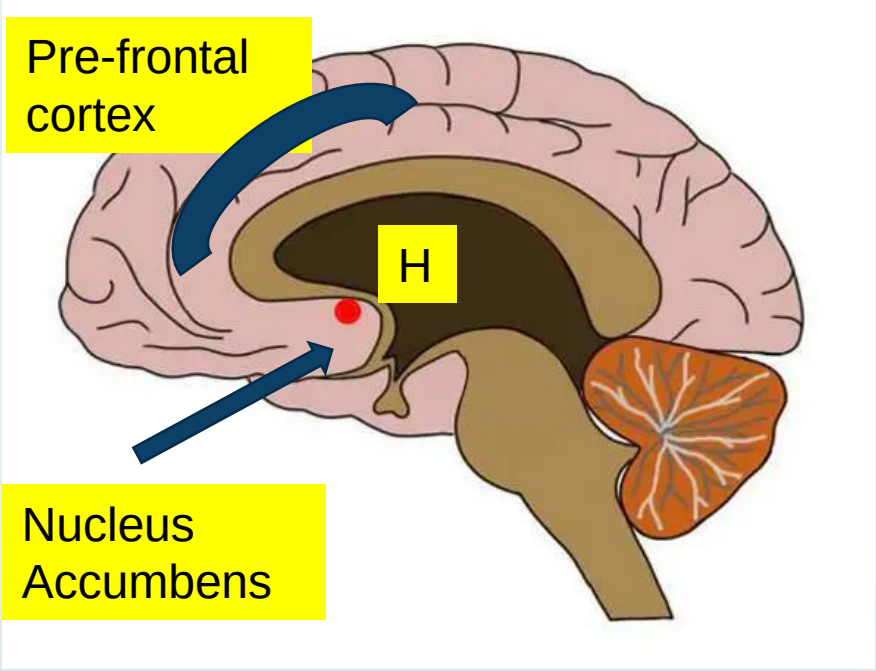
GLP1-RAs: Summary table (p 56 of the CPG)

Drug (SC injection)	Dosage[1]	Mean weight loss vs in excess of placebo[1,2]	Common side effects[2]	Warnings & precautions[3]	Contraindications[2]
Liraglutide	3 mg daily	5.24 kg (% weight loss from baseline: 6-7%)	Nausea, vomiting	• Risk of thyroid C-cell tumours • Acute pancreatitis or GBD • Hypoglycaemia in combination with insulin or secretagogues • Transient worsening of retinopathy (**semaglutide)****	• Caution in renal impairment* • Pregnancy • Personal or family history of MTC or MEN
Semaglutide	2.4 mg weekly Start: 0.25 mg/week Increase 4 weekly x 16 weeks	12.7 kg (% weight loss from baseline: 14.9%)			• eGFR <15 ml/min • Pregnancy • Personal or family history of MTC or MEN

**Post marketing reports of AKI or worsening of CKD. **In T2DM with baseline retinopathy and rapid improvement in glycaemic control. eGFR, estimated glomerular filtration rate; GBD, gall bladder disease; MEN, multiple endocrine neoplasia; MTC, medullary thyroid carcinoma; SC, subcutaneous;*

References: 1. Khera R, et al. JAMA. 2016;315(22):2424-234. 2. Apovian CM, et al. J Clin Endocrinol Metab. 2015;100(2):342-362. 3. Garvey WT, et al. Endocr Pract. 2016;22 Suppl 3:1-203.

The ABCs of Neurobiology



Mesolimbic Reward System

CNS circuit of dopaminergic neurons
dopamine causes ↑ pleasure with intake of ↑ sugar , salt, fat and plays a role in ADDICTION

- Inhibitory control-Pre-frontal cortex
- Reward-Nucleus Accumbens

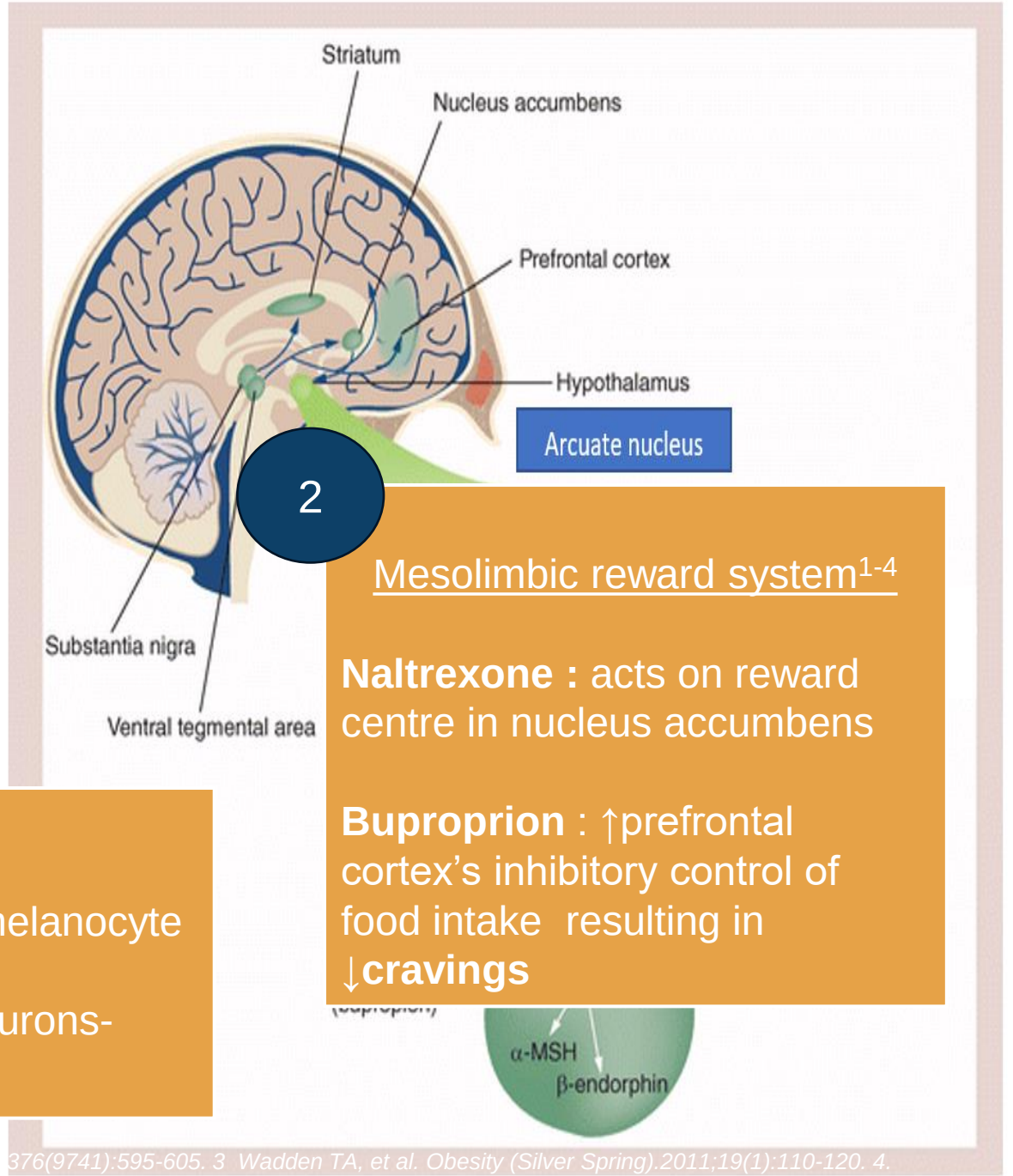
Satiety/Hypothalamus

- Arcuate nucleus
- PVN (paraventricular nucleus/CRH&TRH)
- LH (laternal hypothalamus)

Pharmacotherapy: Mechanism of action

Bupropion/naltrexone

- Bupropion is a dopamine & norepinephrine reuptake inhibitor[1]
- Naltrexone is an opioid antagonist[2]
- Targets 2 areas of the brain giving patients more control of their eating (↓cravings)



1

Arcuate nucleus in the hypothalamus

- **Buproprion**: stimulates POMC neurons to secrete α-melanocyte stimulating hormone & β-endorphins[1]
- **Naltrexone:** attaches to opioid receptors on POMC neurons-blocking autoinhibitory loop[2]

2

Mesolimbic reward system[1-4]

Naltrexone : acts on reward centre in nucleus accumbens

Buproprion : ↑prefrontal cortex's inhibitory control of food intake resulting in **↓cravings**

References: 1. Hollander P, et al. Diabetes Care. Dec 2013;36(12):4022-4029. 2. Greenway FL et al. Lancet. 201 376(9741):595-605. 3 Wadden TA, et al. Obesity (Silver Spring).2011;19(1):110-120. 4. Greenway FL, et al. J Clin Endocrinol Metab. 2009;94(12):4898-4906

Naltrexone/bupropion: Summary table (p 55 of CPG)

Dosage[1]	Mean weight loss vs in excess of placebo[1,2]	Common side effects[2]	Warnings & precautions[3]	Contraindications[2]
High dose: 32/360 mg or 2 tablets 4 times daily	4.95 kg % weight loss from baseline: 5-6%	Nausea, constipation, headache, vomiting, dizziness	Depression Suicidal behaviour & ideation Risk of seizure*, ↑ BP and heart rate**, and hepatotoxicity	Pregnancy Uncontrolled hypertension Seizure disorders Anorexia nervosa or bulimia Drug/alcohol withdrawal MAO inhibitors Chronic opioid use Glaucoma

**Hence, adhere to dosing schedule & avoid co-administration with high-fat meals. **Careful monitoring if used for patients with cardiovascular disease.*

CONTRAVE dose escalation schedule (2.1):

	Morning Dose	Evening Dose
Week 1	1 tablet	None
Week 2	1 tablet	1 tablet
Week 3	2 tablets	1 tablet
Week 4 – Onward	2 tablets	2 tablets

References: 1. Khera R, et al. JAMA. 2016;315(22):2424-234. 2. Apovian CM, et al. J Clin Endocrinol Metab. 2015;100(2):342-362. 3. Garvey WT, et al. Endocr Pract. 2016;22 Suppl 3:1-203.

Key learning points

- Pharmacotherapy for obesity is indicated and effective in **BMI >30kg/m^2 or BMI >27.5kg/m^2 with comorbidities**
- Pharmacotherapy for obesity should only be an **adjunct to lifestyle/ behavioural modifications**
- 5 US-FDA approved drugs for chronic management of obesity
  - orlistat
  - phentermine/topiramate
  - naltrexone/bupropion, and
  - high-dose liraglutide and semaglutide

Key learning points

- **Phentermine monotherapy** indicated only for **short-term management of obesity**, i.e. < 3 months and/or in a cyclical manner
- No RCTs with head-to-head comparisons BUT high-dose semaglutide 2.4 mg weekly & phentermine/topiramate result in most weight loss of >10%
- Careful consideration of the side effects of these drugs is required before initiation
- Liraglutide & semaglutide have added benefit of improving glycaemic control, cardiorenal outcomes & metabolic dysfunction-associated steatotic liver disease (MASLD) in patients with both T2DM + obesity