Update on Obesity Management Pharmacologic Therapies

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Disclosure

Faculty: Bovornpat Suriyapakorn

Relationships with commercial interests:

- Speakers: DKSH

Managing potential bias

- Relationships do not affect my choices in developing content.

Obesity

Chronic Inflammatory Disease

Multifactorial

- Behavioral
- Physiological
- Metabolic
- Cellular
- Molecular

News > Medscape Medical News > Conference News > American Medical Association (AMA) 2013 Annual Meeting

AMA Declares Obesity a Disease

Marcia Frellick
June 19, 2013

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CHICAGO — Physicians voted overwhelmingly to label obesity as a disease that requires a range of interventions to advance treatment and prevention.

However, there was impassioned debate in the hours before the vote here at the American Medical Association (AMA) 2013 Annual Meeting.

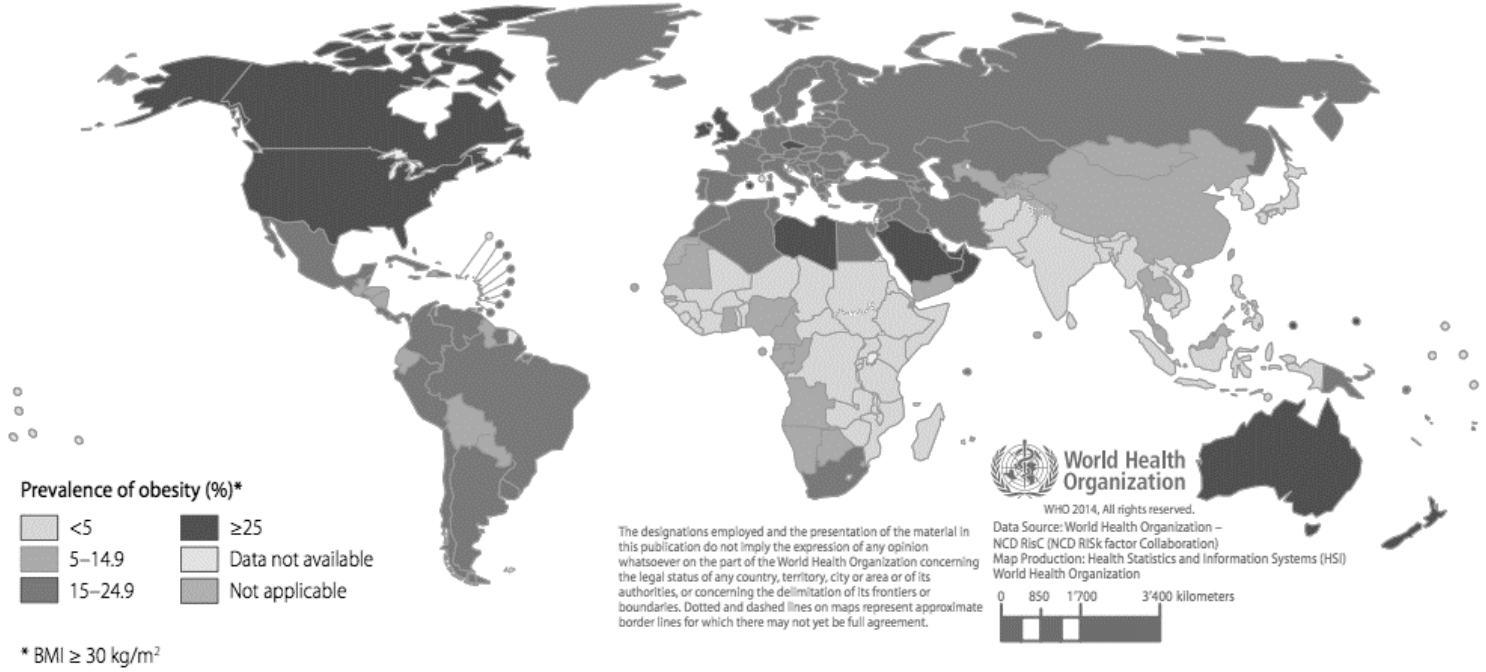
Although policies adopted by the House of Delegates have no legal standing, decisions are often referenced in influencing governmental bodies. This decision could have implications for provider reimbursement, public policy, patient stigma, and *International Classification of Diseases* coding.

"Obesity is a pathophysiologic disease. There is a treatment for this disease; it involves behavioral modifications, medications, and surgeons. Obesity affects minorities disproportionately," said Jonathan Leffert, MD, alternate delegate for Endocrinology, Diabetes, and Metabolism. "The scientific evidence is overwhelming."

NYTimescom. 2013 Available at: http://nyti.ms/1Guko03.

Obesity

Fig. 7.1 Age-standardized prevalence of obesity in men aged 18 years and over (BMI ≥30 kg/m²), 2014



Year	Percentage of obesity	
	25 kg/m²	30 kg/m²
1991	18.2	3.5
1997	24.1	5.8
2004	28.1	6.9
2009	36.5	9.0

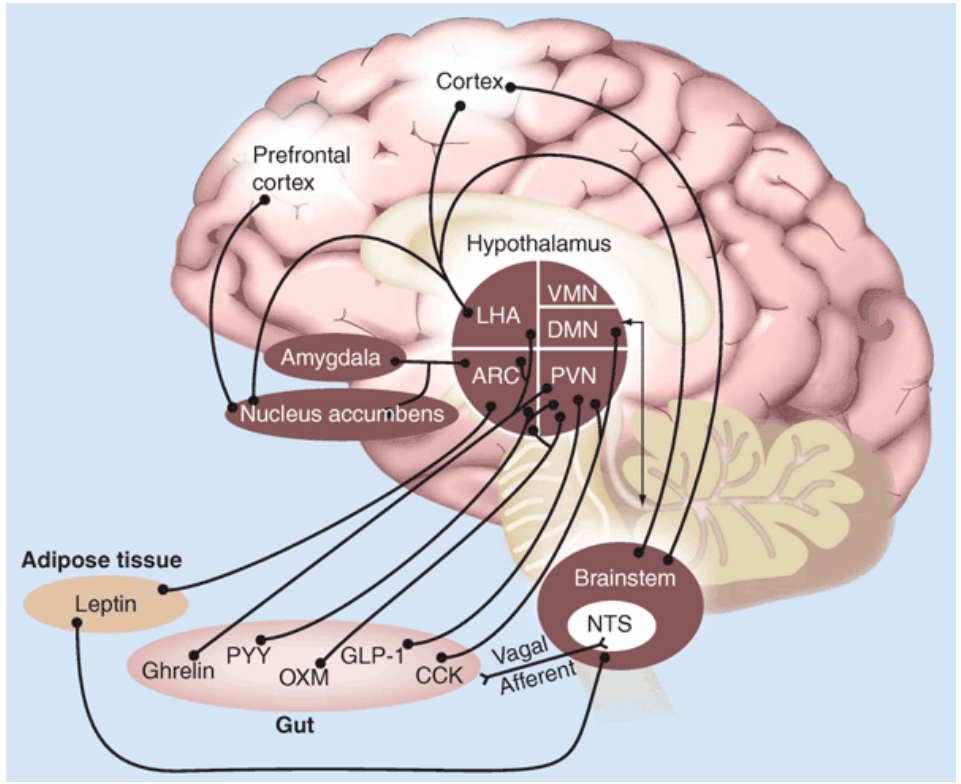
Global Status Report on Noncommunicable Diseases 2014.
Obes Rev 2009;10:589-92.

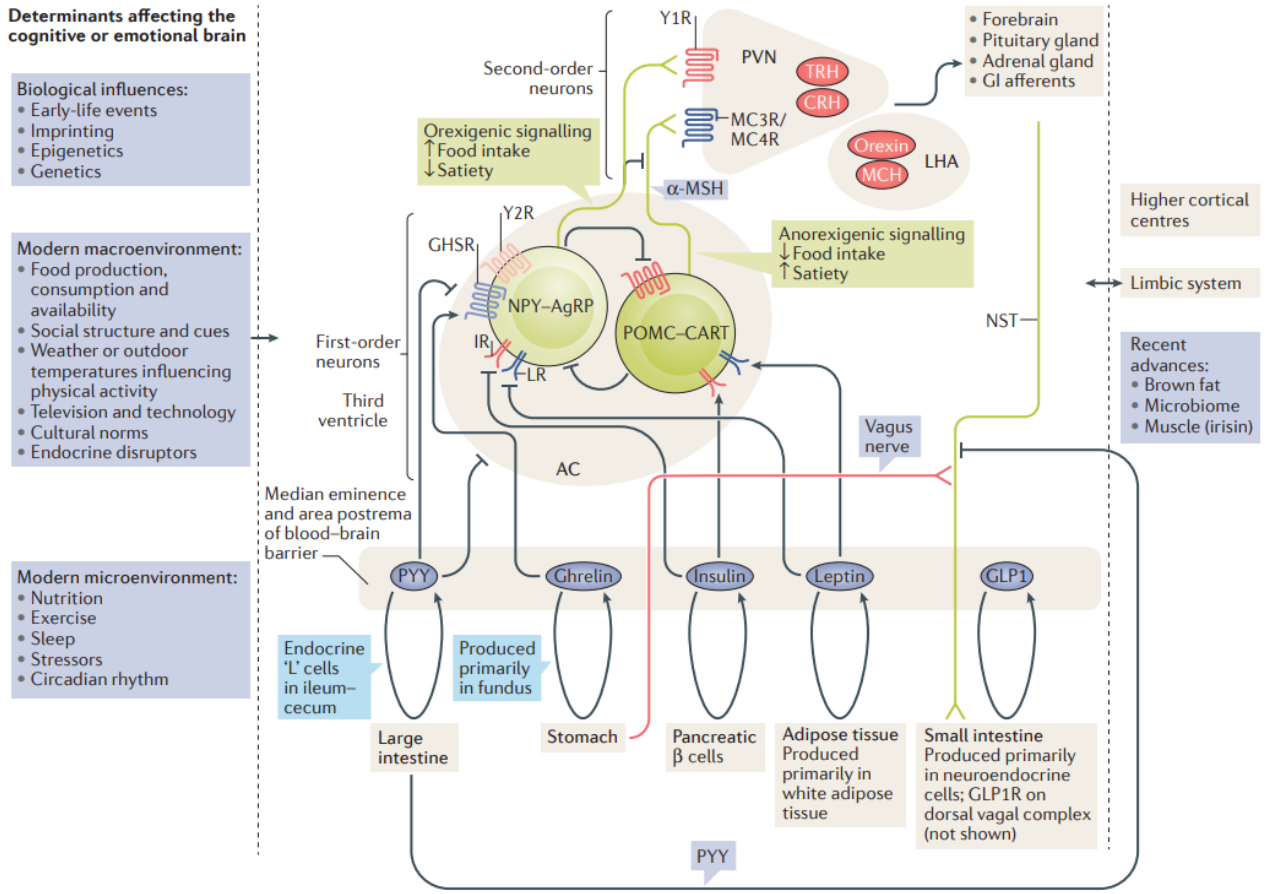
Obesogenic Factors

Weight gain

Due to reduced metabolic rate	Due to increased intake	Due to reduced energy expenditure
Age, sex, genetics, neuroendocrine factors, prandial thermogenesis, brown fat, sarcopenia, post-weight loss, medications	Sociocultural factors, knowledge deficit, saboteurs, mindless eating, physical hunger, emotional eating, psychiatric disorders, sleep deprivation, medications	Sociocultural factors, physical limitations, chronic fatigue, musculoskeletal pain, cardiorespiratory, emotional barriers, psychiatric disorders, medications

The Brain





Nat Rev Endocrinol 2018;14(1):12-24.
Expert Rev Endocrinol Metab 2008;3:577–92.

Orexigenic and Anorexigenic

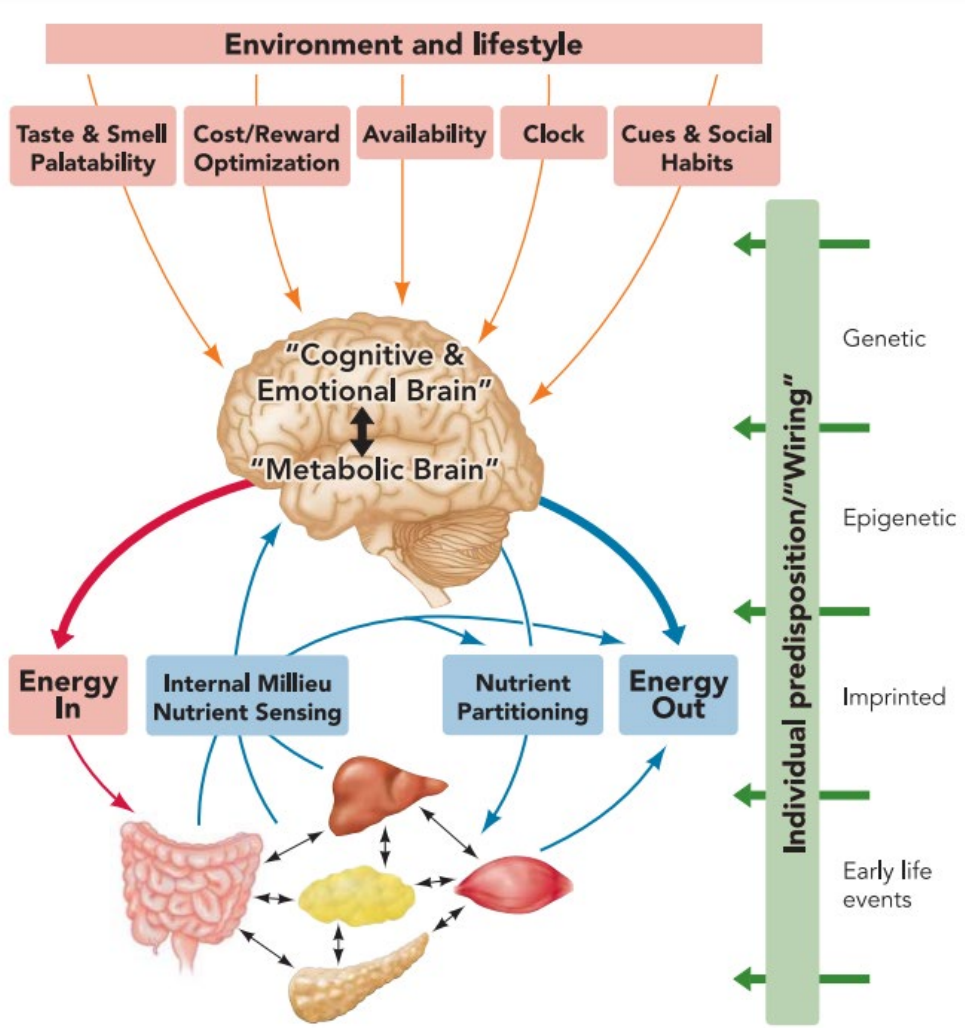
Positive energy balance	Negative energy balance
Proximal NPY, AgRP, Orexin A and B, MCH, Norepinephrine (α2, β), Endocannabinoids	**Proximal** POMC/α-MSH, CART, Norepinephrine (α1)
Distal Ghrelin	**Distal** CCK, GLP-1, Oxyntomodulin, PYY, Amylin, Adiponectin, Pancreatic polypeptide PP, Serotonin, Insulin, Leptin

Cell Metab 2009;9(6)489-98.

Reward System

Food Addiction

- Dopaminergic system
- Opioidergic system
- Cannabinoid system

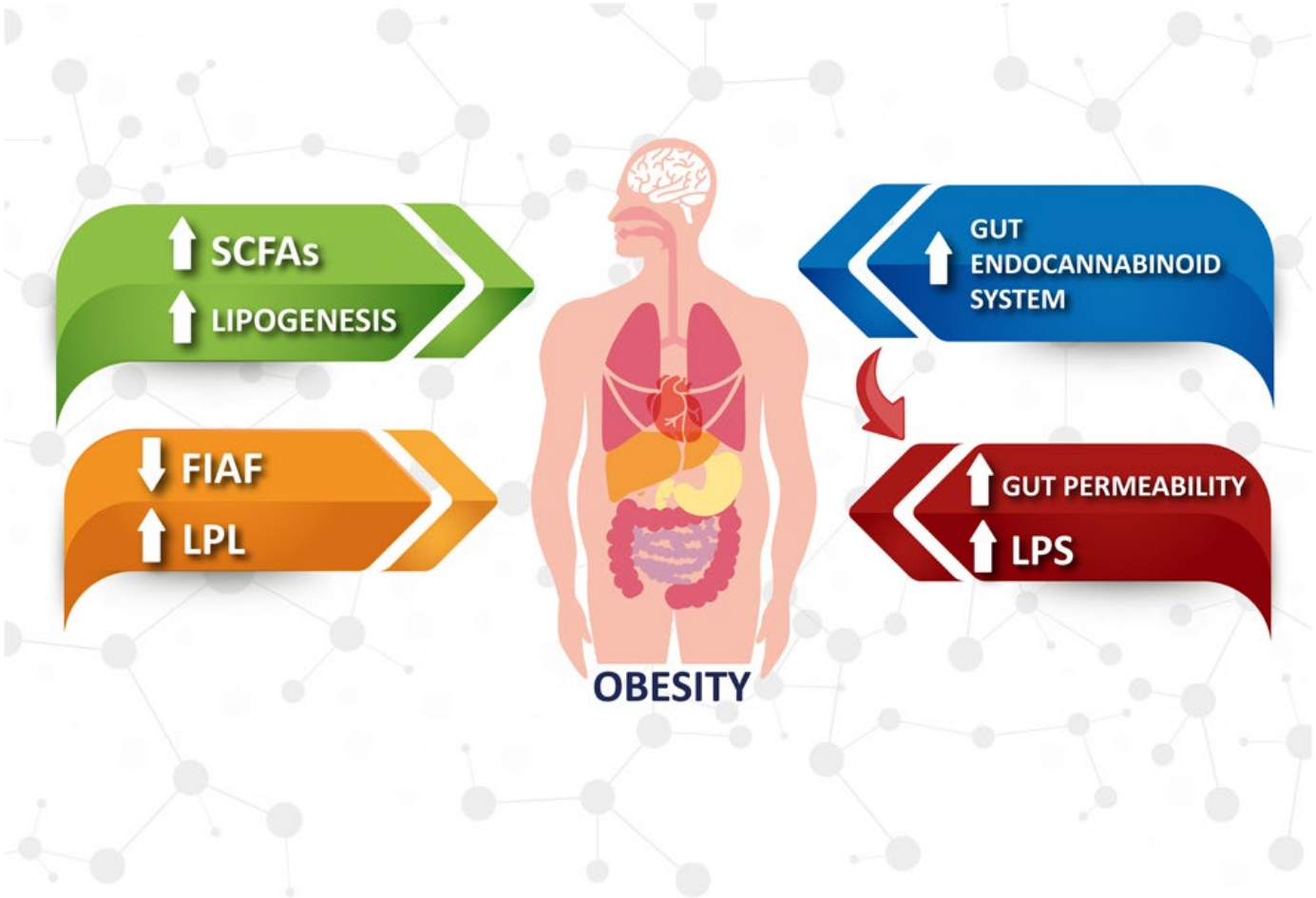


Physiology (Bethesda) 2008;23:75-83.

Gut

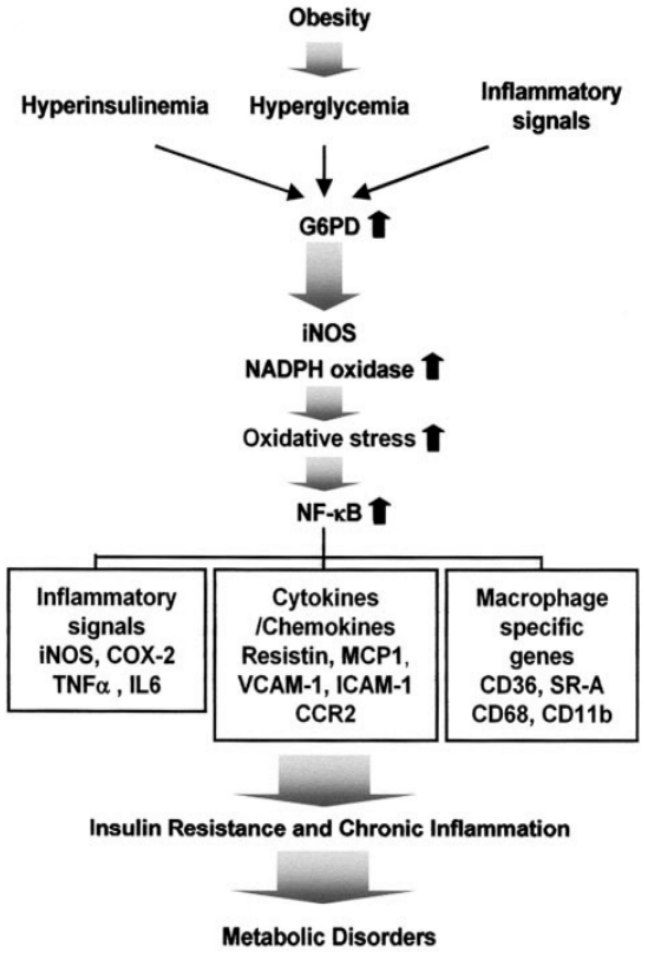
Gut Microbiota

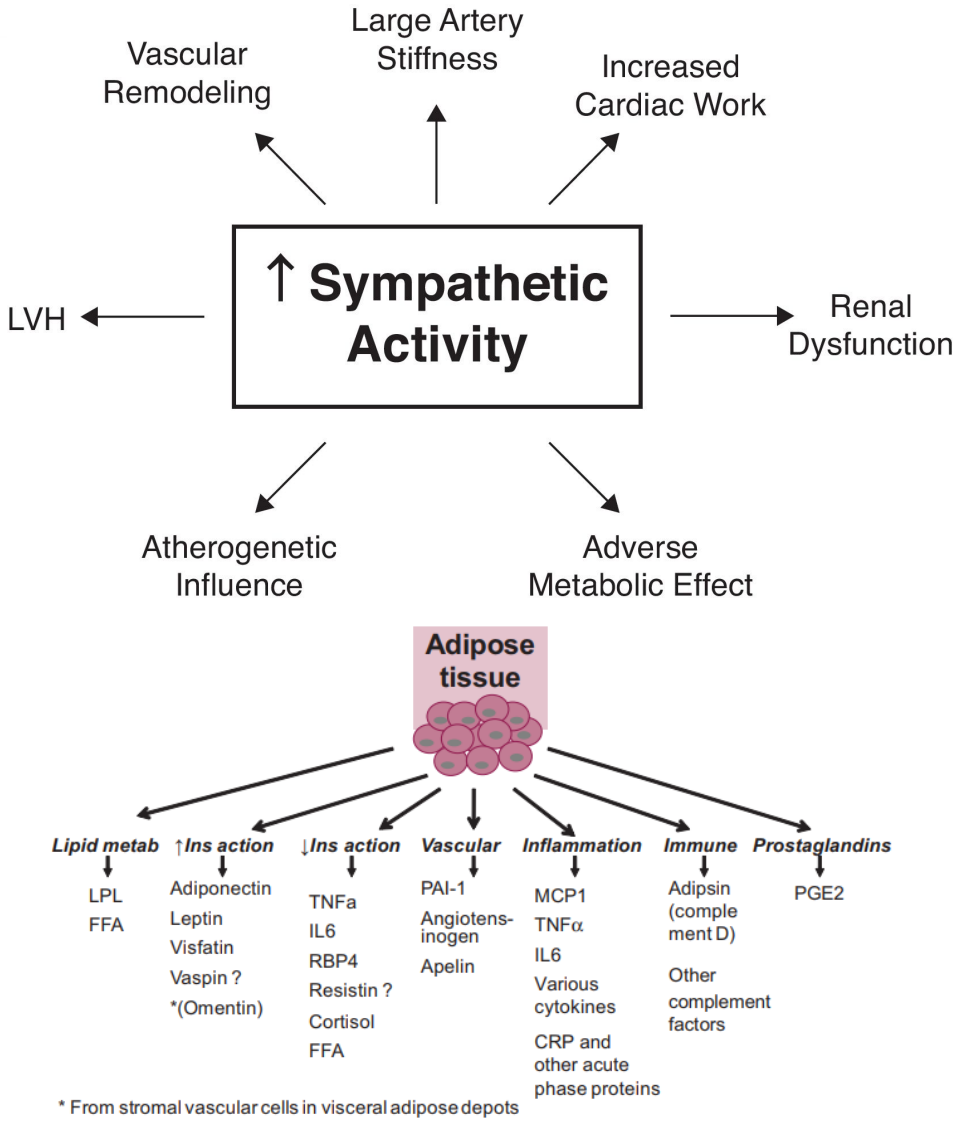
- Inflammation
- Insulin resistance
- Glucose metabolism
- Hepatic lipid metabolism

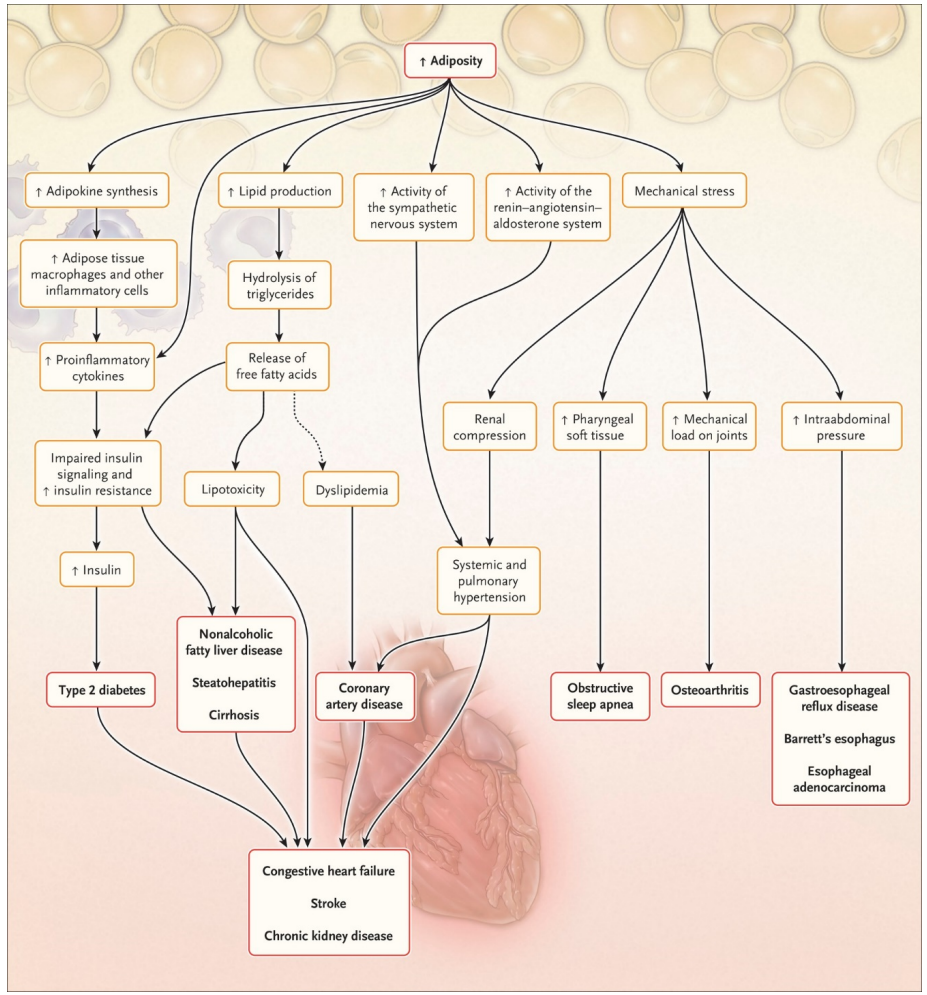


Int J Obes Suppl 2019;9:10-9.
Lancet Gastroenterol Hepatol 2017;2(10):747-56.

Consequences







Diabetes 2006;55:2939–49.
Br J Diabet Vasc Dis 2011;11:55–61.
N Engl J Med 2017;376(3):254-66.

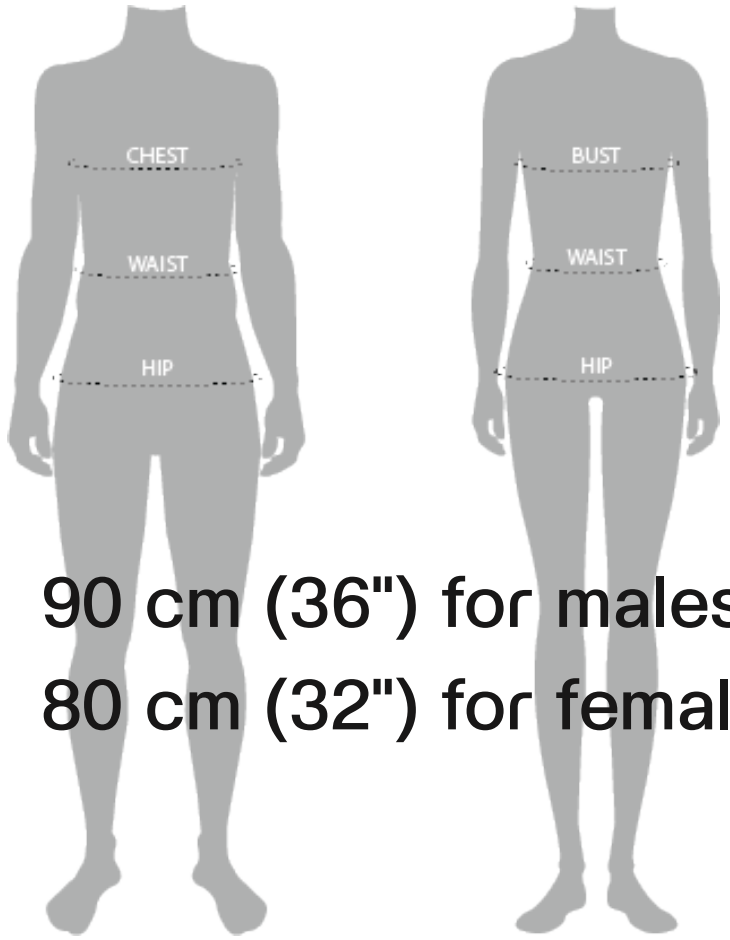
Body Mass Index

Correlate with mortality rate and have developed into an indicator of risk of diseases related to adiposity

Classification	BMI (kg/m^2)	Asian BMI (kg/m^2)
Underweight	<18.5	<18.5
Normal	18.5-24.9	18.5-22.9
Overweight	≥25	≥23
Pre-obesity	25-29.9	23-24.9
Obese type I (obese)	30-34.9	25-29.9
Obese type II (severe obese)	35-39.9	≥30
Obese type III (morbid obese)	≥40	

Lancet 2004;363(9403):157-63.
Diabetes Care 2016;39 (Suppl 1):S47-51.

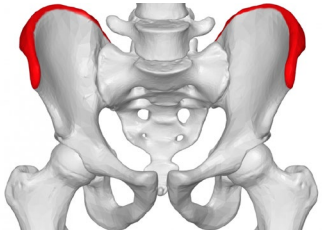
Waist Circumference



90 cm (36") for males

80 cm (32") for females

Measure the narrowest section of the torso, or at the mid point between the top of the hipbones and below the lowest palpable rib.

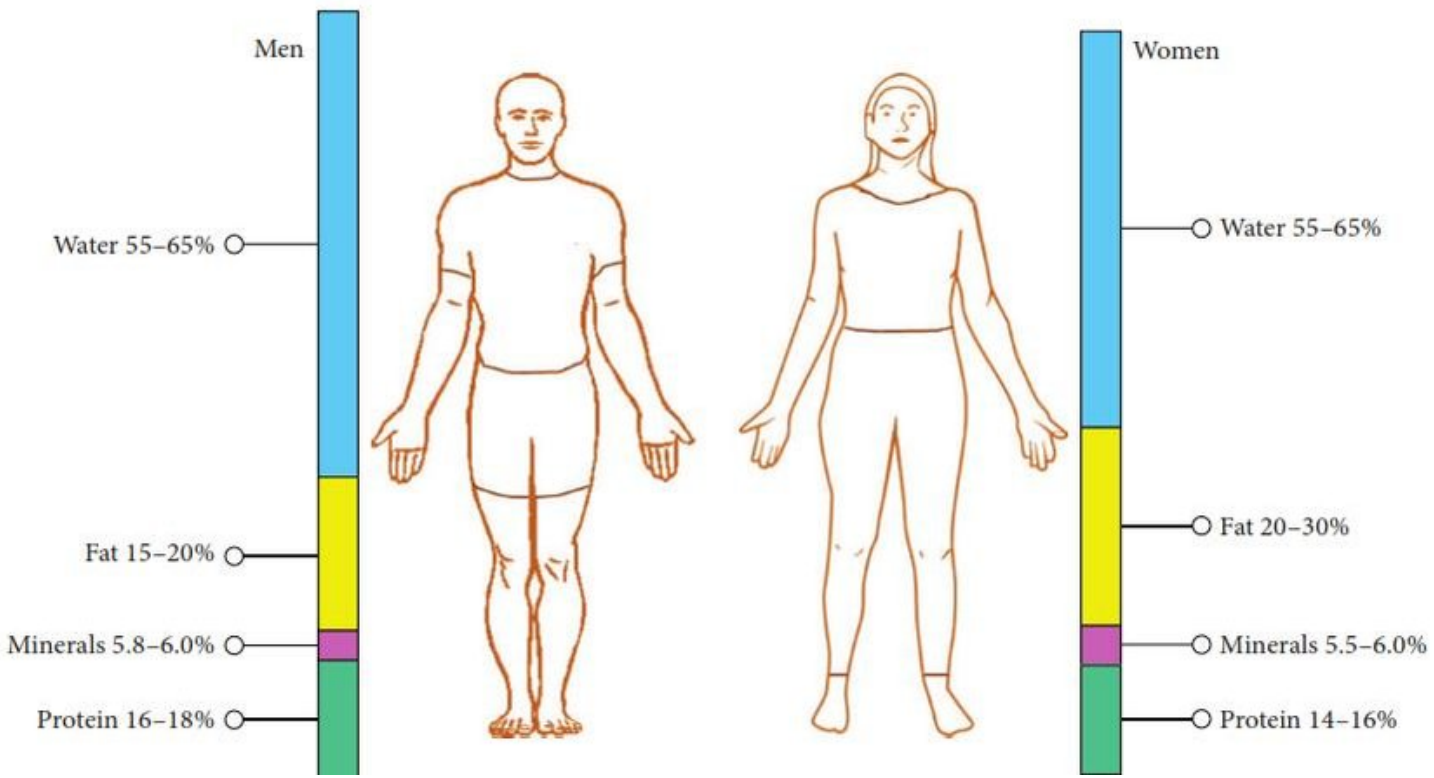


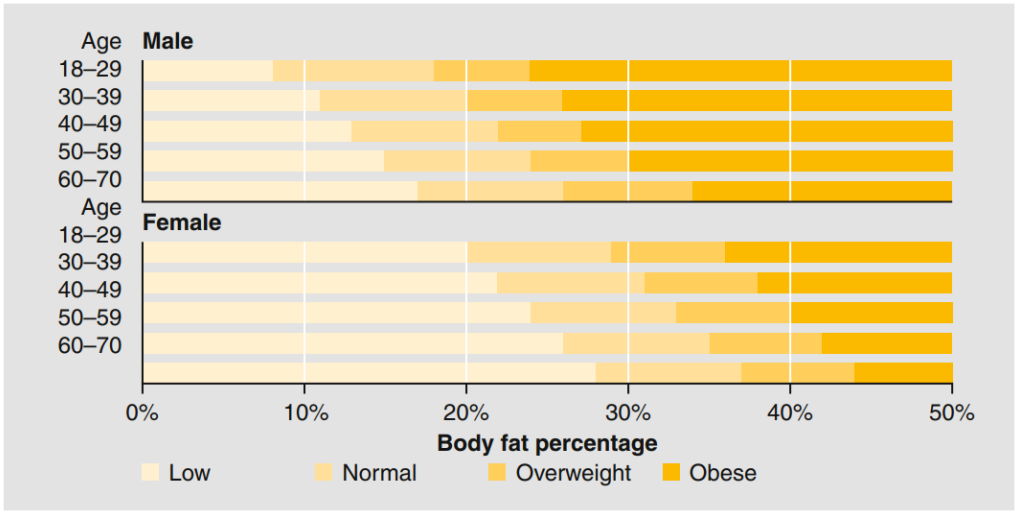
BMI (kg/m^2)	Normal WC	High WC
<18.5	-	-
18.5-22.9	-	-
23-24.9	Increased	High
25-29.9	High	Very high
≥30	Very high	Extremely high

World Health Organ Tech Rep Ser 2000;894:i-xii, 1-253.
Lancet 2004;363(9403):157-63.
Lancet 2005;366:1059-62.

Body Composition

Total Body Water | Fat Mass | Fat Free Mass





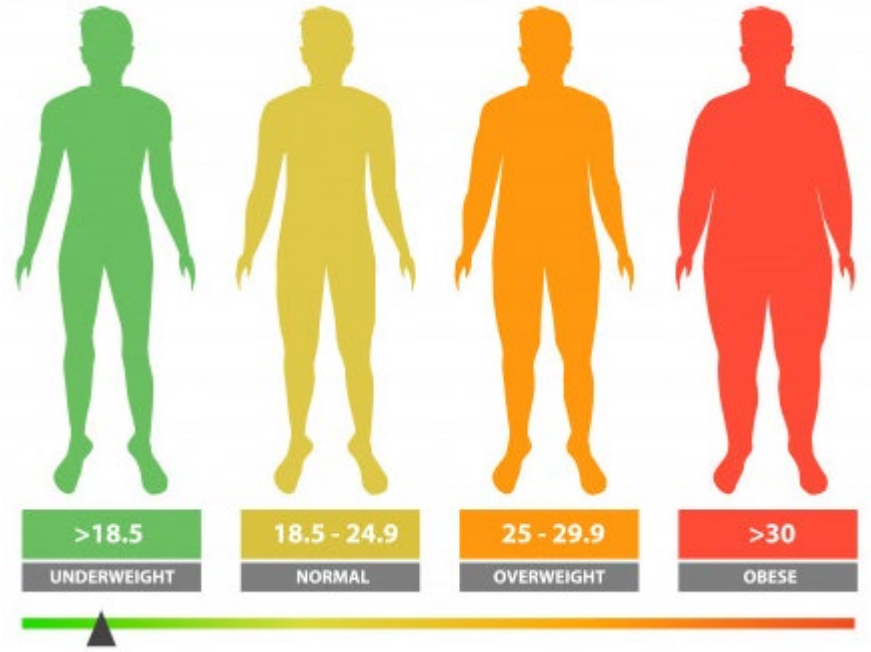
>20% for males

>30% for females

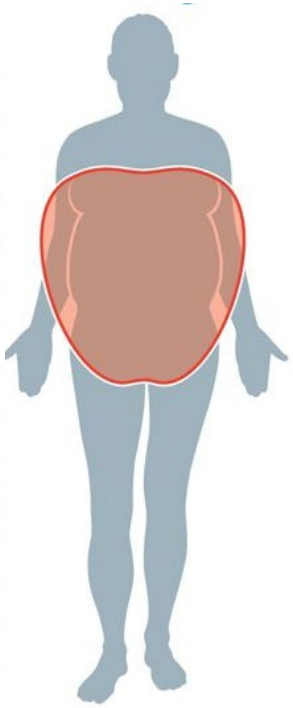
J Med Eng 2014;2014:381251.

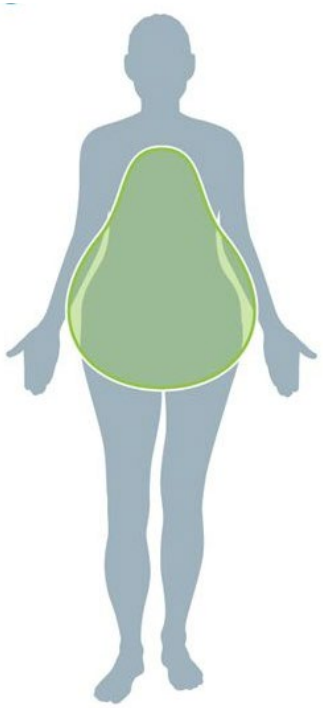
Classification

BMI



Body Shape





Composition

- Dual-energy X-ray absorptiometry (DEXA)
- Computed tomography scan (CT scan)
- Magnetic resonance imaging (MRI)
- Bioelectrical impedance (BIA)
- Hydrostatic weighing

Edmonton Obesity Staging System

More stringent predictor of total mortality than BMI

Stage	Description
0	No apparent obesity-related risk factors, physical symptoms, psychopathology, functional limitations, and/or impairments of well-being
1	Presence of obesity-related subclinical risk factors, mild physical symptoms, mild psychopathology, mild functional limitations, and/or impairment of well-being
2	Presence of established obesity-related chronic disease, moderate limitations in activities of daily living, and/or well-being
3	Established end-organ damage, significant psychopathology, significant functional limitations, and/or impairment of well-being
4	Severe (potentially end-stage) disabilities from obesity-related chronic diseases, disabling psychopathology, functional limitations, and/or impairment of well-being

Int J Obes 2009;33:289-95.

Goal of Therapy

Improve obesity-related comorbid conditions

Reduce the risk of developing future comorbidities

Quality of life **Stigma and Cosmetic**

‘No Ideal Weight’

5%-10% of the baseline weight over 6 months period

Pharmacologic Therapies

Comorbidities
e.g. HT, DM, DLP

	BMI (kg/m^2)				
	≥23 or 25-26.9	27-29.9	30-34.9	35-39.9	≥40
Therapeutic lifestyle changes	✓	✓	✓	✓	✓
Medications		✓	✓	✓	✓
Surgery				✓	✓

Obes Surg 2010;20:929-36.
Diabetes Care 2016;39 (Suppl 1):S47-51.

Pharmacologic Therapies

For each medication prescribed, practitioner should first:

1. Know and understanding primary mechanism
2. Know and understanding indications, contraindications, benefits, risks and side effects
3. Establish a plan for monitoring and follow up
4. Discuss all the above with the patient

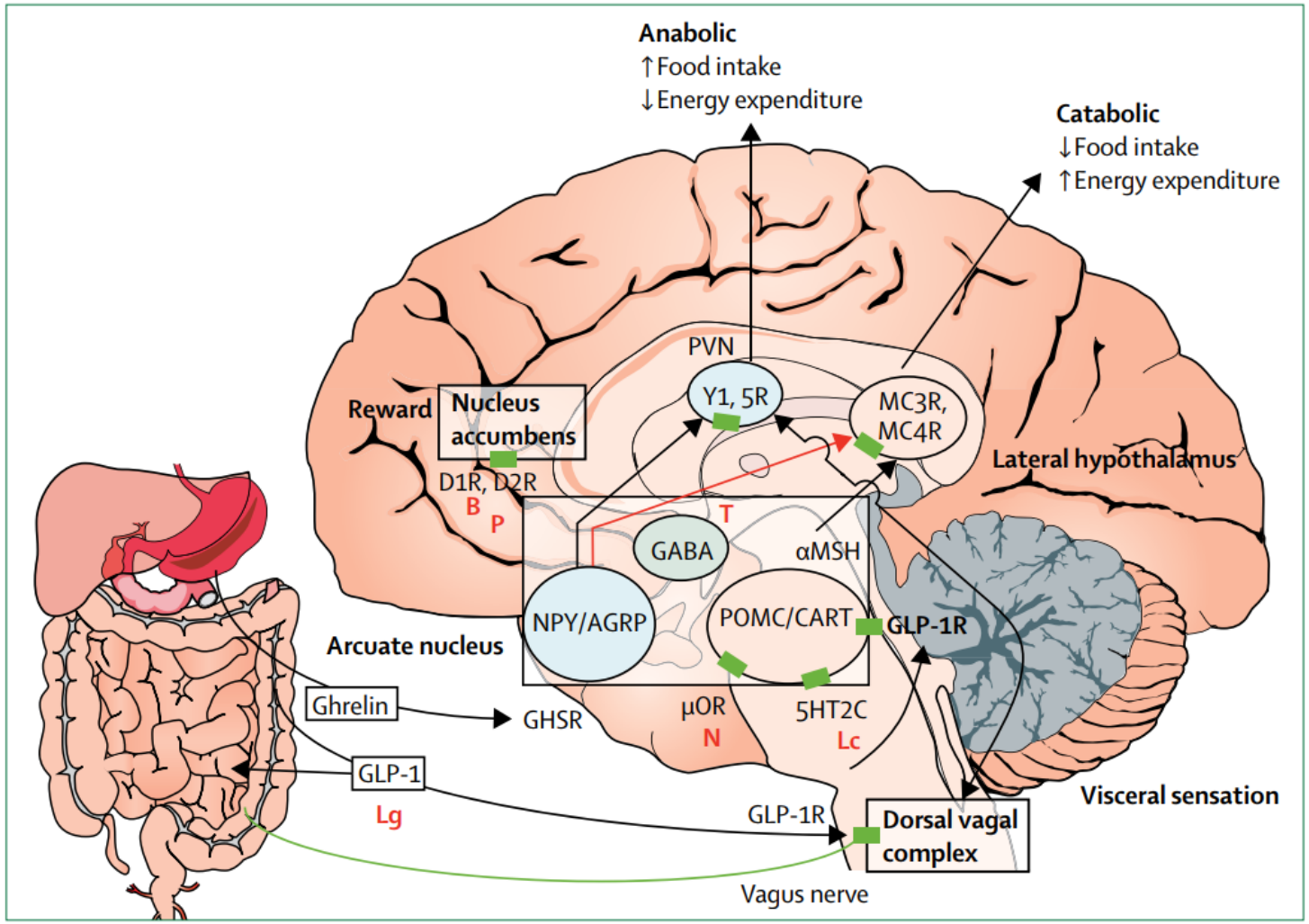
Table 1. History of prescription antiobesity drugs.

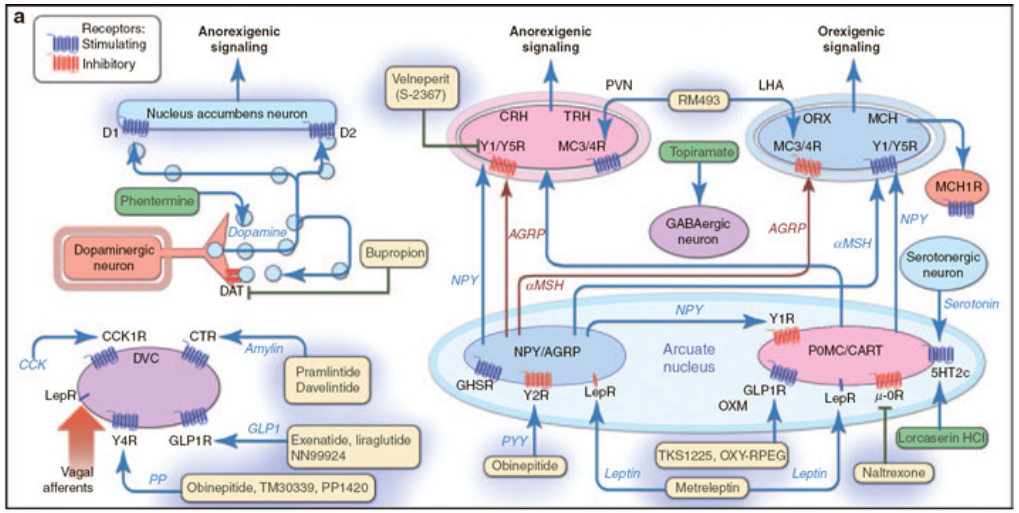
Drug	Year initially approved	Comments
Phentermine	1959	Short-term use; most prescribed drug in the US; withdrawn in Europe in 2000 for unfavorable benefit-to-risk
Diethylpropion	1959	Short-term use
Phendimetrazine	1959	Short-term use
Benzphetamine	1960	Short-term use
Mazindol	1973	Short-term use; discontinued in 1999
Fenfluramine	1973	Short-term use; withdrawn in 1997 due to increased risk of valvular heart disease
Dexfenfluramine	1996	Long-term use; withdrawn in 1997 due to increased risk of valvular heart disease
Sibutramine	1997	Long-term use; withdrawn in 2010 due to increased risk of major adverse cardiovascular events
Orlistat	1999	Long-term use; Approved in 2003 for pediatric obesity[a]
Rimonabant	2006	Long-term use; approved in Europe only; withdrawn in 2008 due to serious psychiatric adverse events
Phentermine + Topiramate	2012	Long-term use; marketed under REMS[b] to reduce teratogenicity risk
Lorcaserin	2012	Long-term use; marketing delayed by a year due to DEA classification process
Naltrexone + Bupropion	2014	Long-term use
Liraglutide 3.0 mg	2014	Long-term use; also approved at a lower dose for type 2 diabetes in 2010

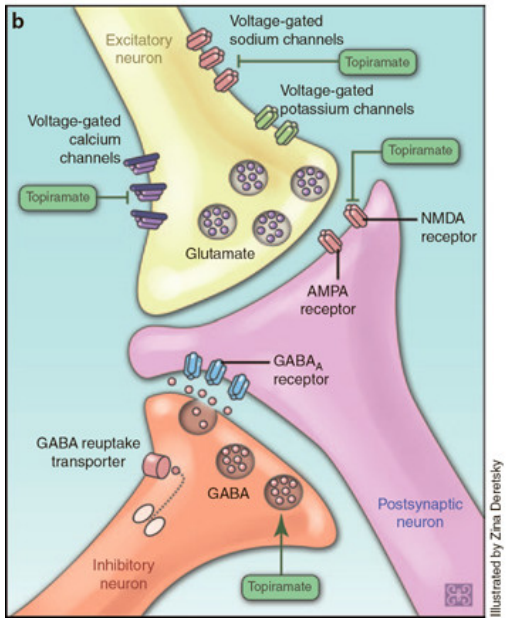
[a] Alli is lower-dose (60 mg) orlistat approved in 2007 for use without prescription.
[b] REMS, Risk Evaluation and Mitigation Strategy.

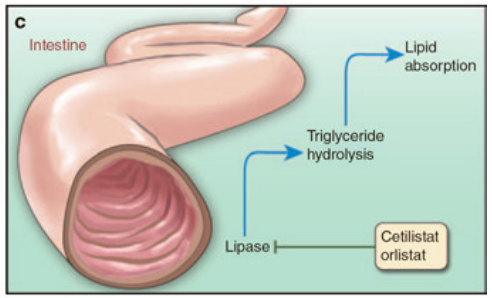
Clin Chem 2018;64(1):118-29.

Pharmacologic Therapies









1. Manipulate CNS
2. Endocrine agents
3. Other cause of action

Lancet Diabetes Endocrinol 2018;6(3):237-48.
Clin Pharmacol Ther 2014;95(1):53-66.

Sibutramine

Abbott to Voluntarily Withdraw Meridia® (Sibutramine) in the U.S.

Oct 8, 2010 12:01pm

ABBOTT PARK, Ill., Oct. 8 /PRNewswire/ -- Abbott (NYSE: ABT) will voluntarily withdraw Meridia® (sibutramine) from the U.S. market at the request of the U.S. Food and Drug Administration (FDA).

The FDA's request is based primarily on the results of the SCOUT (Sibutramine Cardiovascular OUTcome Trial) study, an approximately 10,000 patient, 6-year study requested by European regulatory authorities as a post-marketing commitment to evaluate cardiovascular safety in high-risk patients. The majority of these patients had underlying cardiovascular disease and were not eligible to receive sibutramine under the current labeling.

The SCOUT results are in contrast to the vast body of sibutramine data for the on-label patient population, including 46 controlled clinical trials and more than 6 million patient years of use accumulated over 13 years during which the product has been available. These data fail to confirm the excess cardiovascular risk found in the SCOUT study.

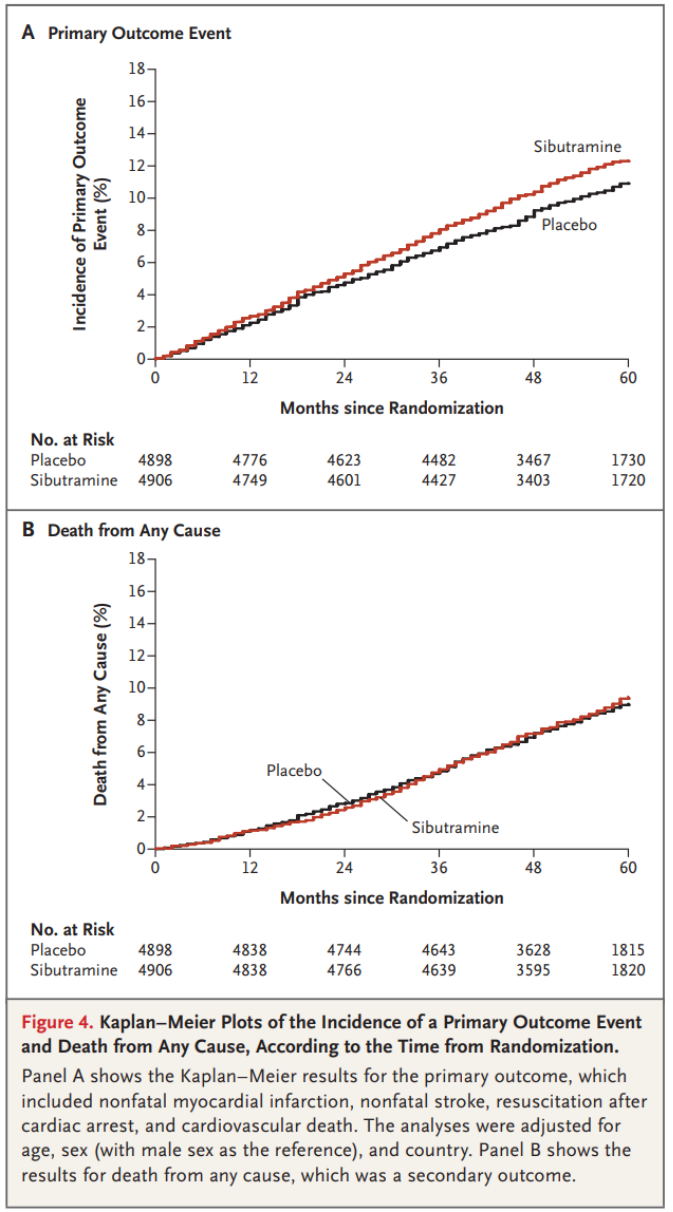
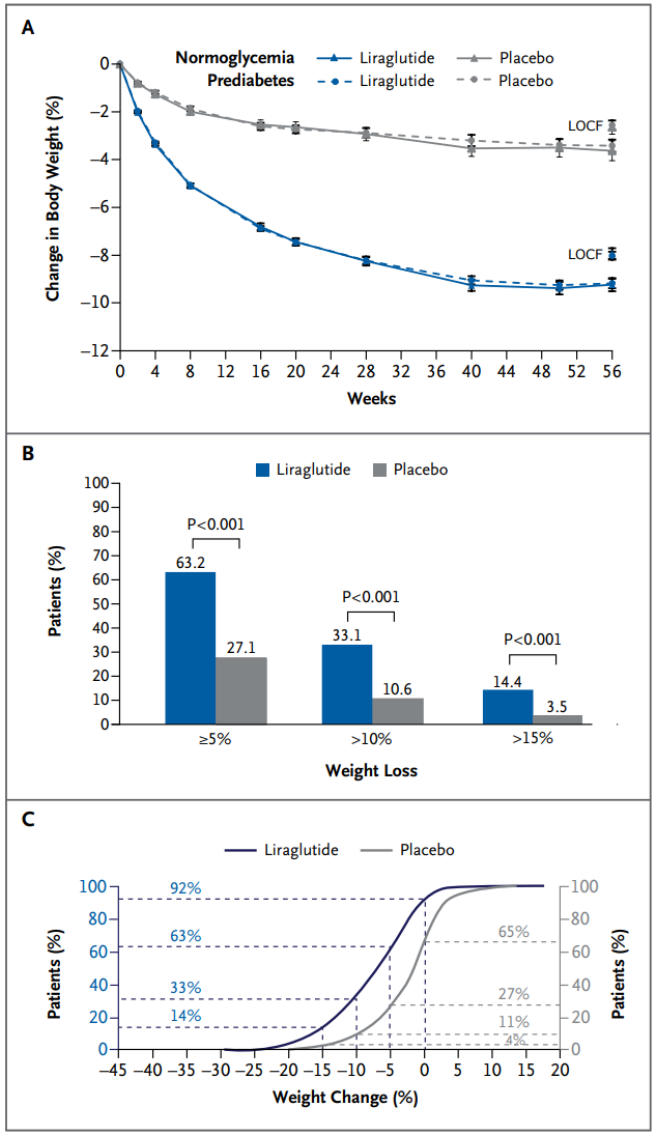


Figure 4. Kaplan–Meier Plots of the Incidence of a Primary Outcome Event and Death from Any Cause, According to the Time from Randomization.
Panel A shows the Kaplan–Meier results for the primary outcome, which included nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest, and cardiovascular death. The analyses were adjusted for age, sex (with male sex as the reference), and country. Panel B shows the results for death from any cause, which was a secondary outcome.

US FDA
N Engl J Med 2010;363(10):905-17.

Liraglutide

- Glucagon-like peptide-1 (GLP-1) agonist
- Long-term treatment
- Efficacy
  - SCALE Obesity and Prediabetes 1-yr
    - 8.4 kg (8%) VS 2.8 kg (2.6%)
    - ≥5% weight loss 63.2% VS 27.1%
    - ≥10% weight loss 33.1% VS 10.6%
  - SCALE Maintenance trial 1-yr
    - 6 kg (6.2%) VS 0.1 kg (0.2%)
    - ≥5% weight loss 50.5% VS 21.8%
    - ≥10% weight loss 26.1% VS 6.3%



Lancet Diabetes Endocrinol 2018;6(3):237-48.
Clin Pharmacol Ther 2014;95(1):53-66.
N Engl J Med 2015;373(1):11-22.
Int J Obes (Lond) 2013;37(11):1443-51.

Liraglutide

- Pregnancy, Hx or FH of medullary thyroid cancer or Multiple Endocrine Neoplasia Syndrome type 2
- GI, increased heart rate, renal insufficiency or failure, suicidal, and hypoglycemia
- DM, dose-dependent and duration-dependent thyroid C-cell tumors, Hx of pancreatitis, and gallstone
- Absorption of oral medications

Orlistat

- Potent, selective inhibitor of up to 91.4% of gastric and pancreatic lipases
- Non-systemic
- Long-term treatment
- Estimated typical daily caloric deficit of approx. 200 calories
- Fat excreted in a dose-dependent manner, plateau at around 30-35% (dosages 180-360 mg/d)

Orlistat

- Efficacy
  - Weight loss ranged from 4.7-10.3 kg VS 0.9-6.4 kg
  - ≥5% reduction 45.7-65.7% VS 22.6-43.6%
  - ≥10% reduction 26.2-38.9% VS 11.3-24.8%

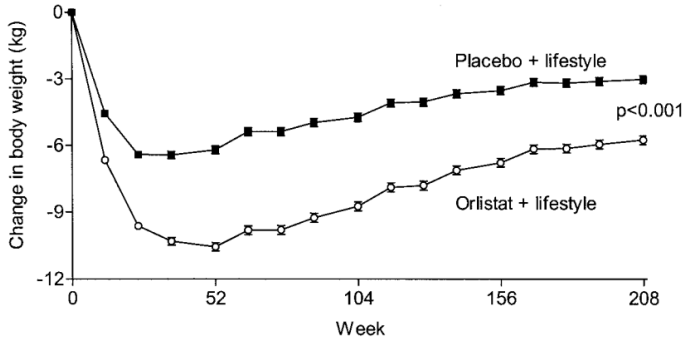


Figure 2—*Weight loss (means ± SEM) during 4 years of treatment with orlistat plus lifestyle changes or placebo plus lifestyle changes in obese patients (LOCF data).*

Study	Duration (wk)	Weight reduction; kg (%)	≥5% reduction (%)	≥10% reduction (%)
Krempf et al.	76	6.4 VS 2.7 (6.5 VS 3.0)	58.3 VS 37.8	33.6 VS 16.8
Hauptman et al.	104	7.9 VS 4.1 (7.9 VS 4.2)	50.5 VS 30.7	28.6 VS 11.3
XENDOS	4-y	6.3 VS 4.1 (6.3 VS 3.7)	52.8 VS 37.3	26.2 VS 15.6

Drugs 2006;66(12):1625-56.
Arch Fam Med 2000;9(2):160-7.
Int J Obes Relat Metab Diord 2003;27(5):591-7.
Diabetes Care 2004;27(1):155-61.

Orlistat

- Efficacy

Study	ITT Weight reduction (kg)	≥5% reduction (%)	≥10% reduction (%)
X-PERT 500 def	8.62	84	50
X-PERT 1,000 def	9.52	85	53
XXL	Not stated	87	50

Diabetes Obes Metab 2005;7(6):699-708.
Diabetes Obes Metab 2005;7(1):21-7.

Orlistat

- Pregnancy, chronic malabsorption syndrome, cholestasis, (and Hx of pancreatitis)
- GI, nephron- and cholelithiasis, and severe liver injury
- Lipophilic drugs e.g. amiodarone
- Warfarin
- Narrow therapeutic drugs e.g. cyclosporin and levothyroxine
- Vitamin supplement
- 60 to 120 mg PO pc within 1-hr three times per day
- Best studied and has lowest risk of long-term side effects

Orlistat

- Tolerability
  - Oily spotting, flatus with discharge, fecal urgency, and fatty/oil stool >20% incidence ⟶ 'treatment effects'
  - Oily evacuation, increased defecation, and fecal incontinence >5% incidence

>80% of users experienced at least one GI AE

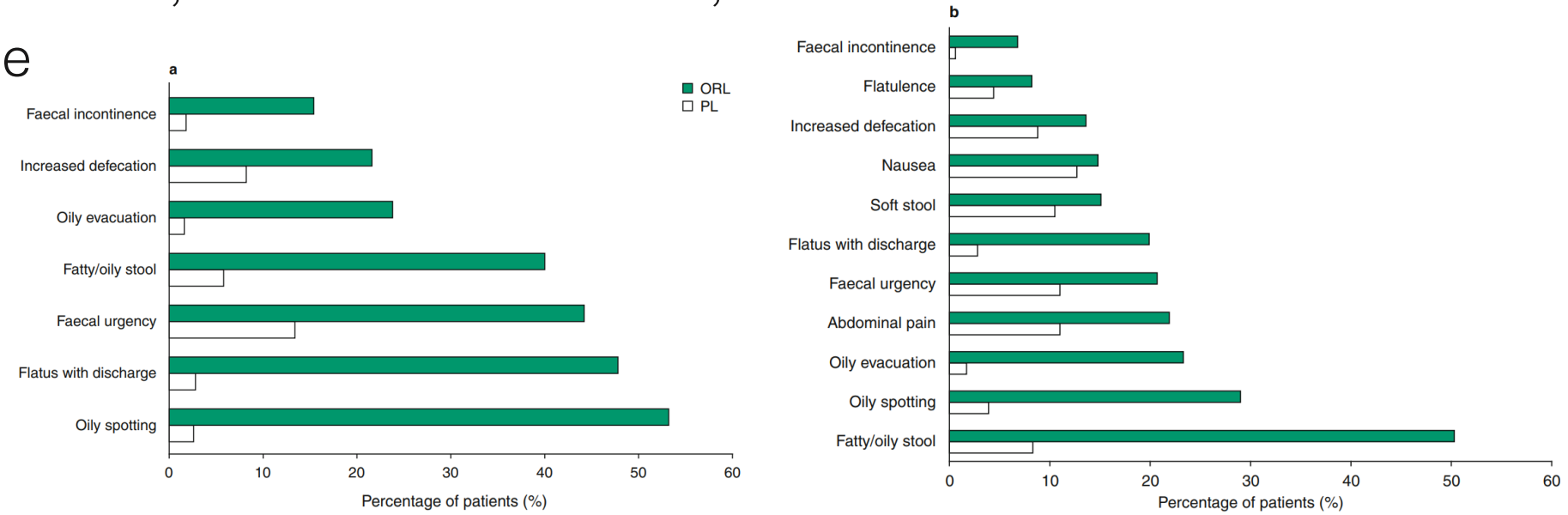


Fig. 4. The tolerability profile of orlistat (ORL) in obese adult and adolescent patients receiving ORL 120mg three times daily. (**a**) Results of a pooled analysis of 1913 and 1466 obese adults receiving ORL or placebo (PL) in seven double-blind, PL-controlled clinical trials[8] and (**b**) results of a randomised, double-blind, PL-controlled clinical trial in 539 obese adolescents receiving ORL or PL. Only descriptive analyses were reported.

Drugs 2006;66(12):1625-56.

Pharmacologic Therapies

Table 2. 1-Year weight loss and secondary efficacy of currently available antiobesity drugs.

Drug	Weight loss relative to placebo	Glycemic measures	Blood pressure	Lipids
Orlistat	Approximately 3.0%	+++[a]	++	++
Lorcaserin	3.0 to 3.6%	+++	+	+
Liraglutide	4.0 to 5.4%	++++	++	++
Phentermine/Topiramate	8.6 to 9.3%	+++	++	++
Naltrexone/Bupropion	3.3 to 4.8%	++	Unfavorable	+

[a]+ least efficacy; +++++ most efficacy.
When several doses have been studied, data are shown for the most effective dose.

Clin Chem 2018;64(1):118-29.

Pharmacologic Therapies

	Duration	Number of patients (placebo/drug)	Weight loss* (placebo/drug)	Proportion of participants who lost ≥5% weight (%; placebo/drug)	Proportion of participants who lost ≥10% weight (%; placebo/drug)	Comments
Orlistat						
Hollander et al (1998)[32]‡	56 weeks	159/163	4·3%/6·2%	22·6%/48·8%	8·8%/17·9%	..
Sjöström et al (1998)[33]	56 weeks	343/345	6·1%/10·2%	..	..	..
Davidson et al (1999)[34]	56 weeks	223/657	2·45%/4%	..	..	..
Finer et al (2000)[35]	56 weeks	114/114	5·4%/8·5%	..	..	..
Rössner et al (2000)[36]	56 weeks	243/244	6·6%/9·7%	..	..	..
Kelley et al (2002)[37]‡	18 months	269/266	1·22%/3·76%	13%/32·7% (at 1 year)	3·7%/10·2% (at 1 year)	HbA_{1c} decrease (placebo/drug): 0·25%/0·56%
Krempf et al (2003)[38]	18 months	350/346	3%/6·5%	46·4%/65·9% (at 1 year)	24·5%/32·9% (at 1 year)	..
Torgerson et al (2004)[39]	4 years	1637/1640	6·2%/10·6% (at 1 year)	45·1%/72·8%	..	37% reduced risk of developing type 2 diabetes
Phentermine-topiramate ER						
Gadde et al (2011)[40]	56 weeks	994/995	1·4/10·2	21%/70%	7%/48%	..
Allison et al (2011)[41]	56 weeks	512/514	1·6%/10·9%	17·3%/66·7%	7·4%/47·2%	..
Lorcasarin						
Smith et al (2010)[42]	56 weeks	1587/1595	2·2%/5·8%	20·3%/47·5%	7·7%/22·6%	1127/2472 (placebo/drug) echocardiograms showed no evidence of valvular heart disease at 1–2 years
Fidler et al (2011)[43]	56 weeks	834/917	2·8%/5·8%	25·0%/47·2%	17·4%/22·6%	..
O'Neil et al (2012)[44]‡	56 weeks	252/256	0·4%/4·5%	16·1%/37·5%	..	HbA_{1c} decrease (placebo/drug): 0·4%/0·9%
Naltrexone-bupropion						
Greenway et al (2010)[45]	56 weeks	581/583	1·3%/6·1%	16%/48%	..	..
Apovian et al (2013)[23]	56 weeks	495/1001	1·2%/6·4%	17·5%/55·6%	..	..
Liraglutide 3 mg						
Astrup et al (2012)[24]	56 weeks	98/371	3·8/5·8†	..	..	Four doses tested, n=90–95 per dose group
Wadden et al (2013)[48]	68 weeks	210/212	0·2%/6·2%	21·8%/50·5%	..	..
Pi-Sunyer et al (2015)[49]	56 weeks	1244/2487	2·8/8·4	27·1%/63·2%	..	..
Davies et al (2015)[25]‡	56 weeks	212/423	2%/6%	21·4%/54·3%	6·7%/25·2%	..
le Roux et al (2017)[50]	3 years	412/714	1·9%/6·1%	23·7%/49·6%	9·9%/24·8%	Reduced risk of progression to type 2 diabetes

For phentermine and orlistat, data are from phase 3 randomised controlled trials; however, not all studies on these drugs are included here. The studies listed for phentermine predate modern FDA standards for clinical trials in support of a weight-loss indication and are presented as examples of the types of studies that were done. For orlistat, although many small studies have been completed, those included in the table enrolled the largest number of patients and were the longest in duration. FDA=US Food and Drug Administration. *Mean % reduction in bodyweight or weight loss in kg. †Data taken from Bray's 2010 chapter that summarises results of a 6 month phentermine study, see references therein. ‡Clinicals trials done exclusively with patients who had type 2 diabetes.

Table 1: **Data supporting the safety and efficacy of FDA-approved anti-obesity drugs**

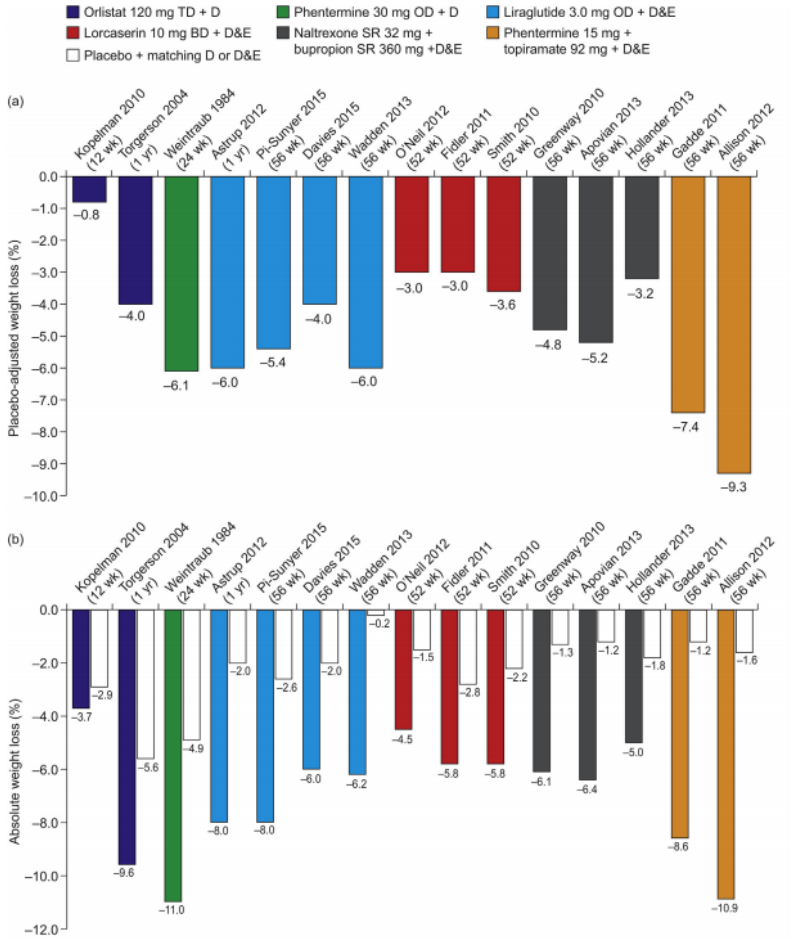
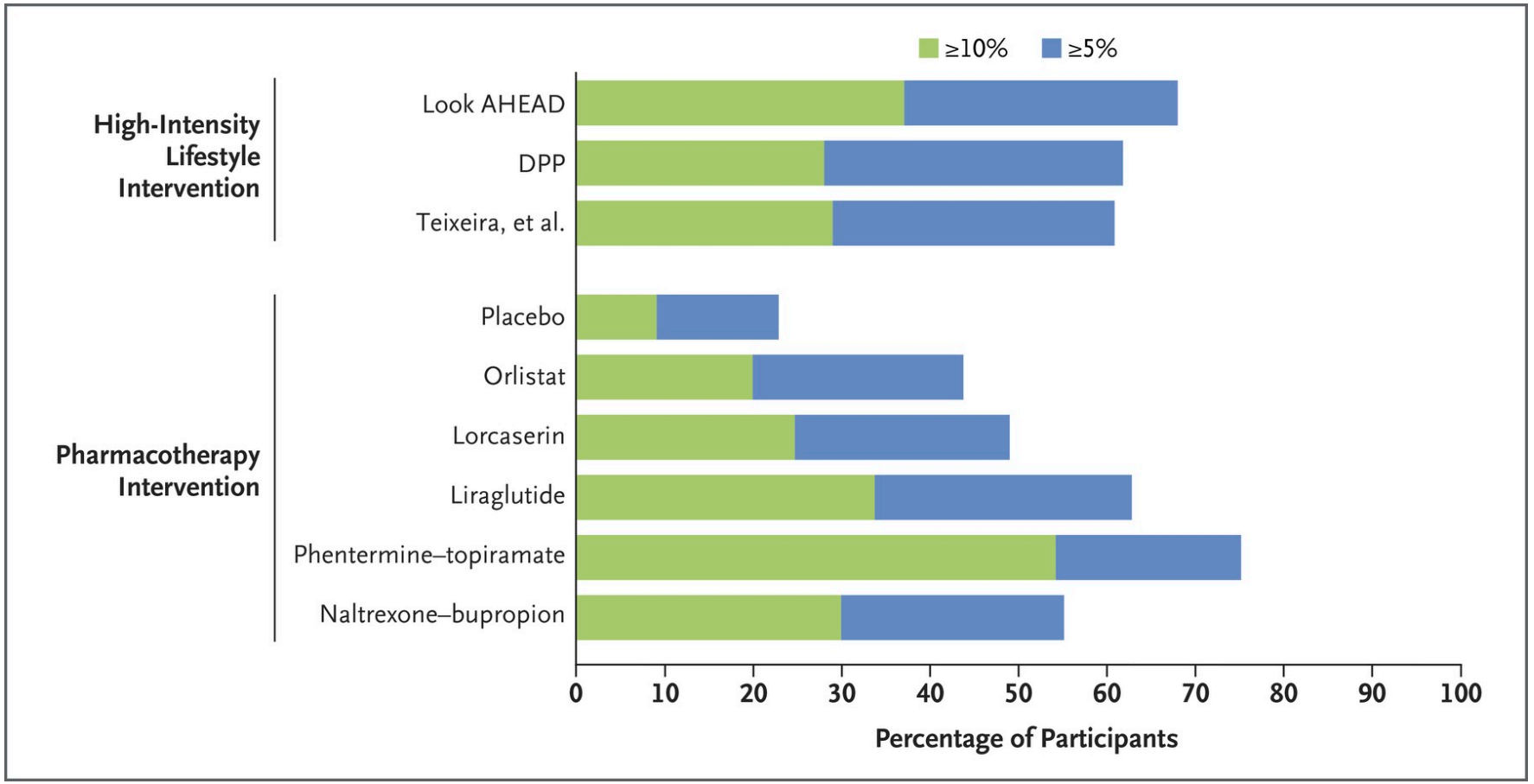


Figure 1 Percentage weight loss with obesity pharmacotherapies: (a) placebo-adjusted percentage weight loss*; (b) absolute percentage weight loss; *Placebo-adjusted % weight loss calculated by subtracting the % weight loss with placebo from the % weight loss with active treatment. Percentage weight losses were calculated for Kopelman et al. [20], Torgerson et al. [21] and Astrup et al. [23] using mean baseline weight and reported absolute weight reductions. In all trials, missing values were imputed using last observation carried forward (LOCF) methods. D, diet; D&E, diet and exercise; OD, once daily; BD, twice daily; TD, three-times daily; Y, year; wk, week.

Lancet Diabetes Endocrinol 2018;6(3):237-48.

Obes Res Clin Pract 2017;11(5):501-21.

Pharmacologic Therapies



N Engl J Med 2017;376(3):254-66.

Pharmacologic Therapies

Practical tips for medication treatment

- Undesirable side effects, contraindications, or drug-drug interaction
- Any of medications could improve another symptom or condition
- Should be used at the lowest effective dose.
- Should be stopped if a ≥4-5% weight loss is not achieved within 3-4 months of the patient using the maximum-tolerated dose.

Pharmacologic Therapies

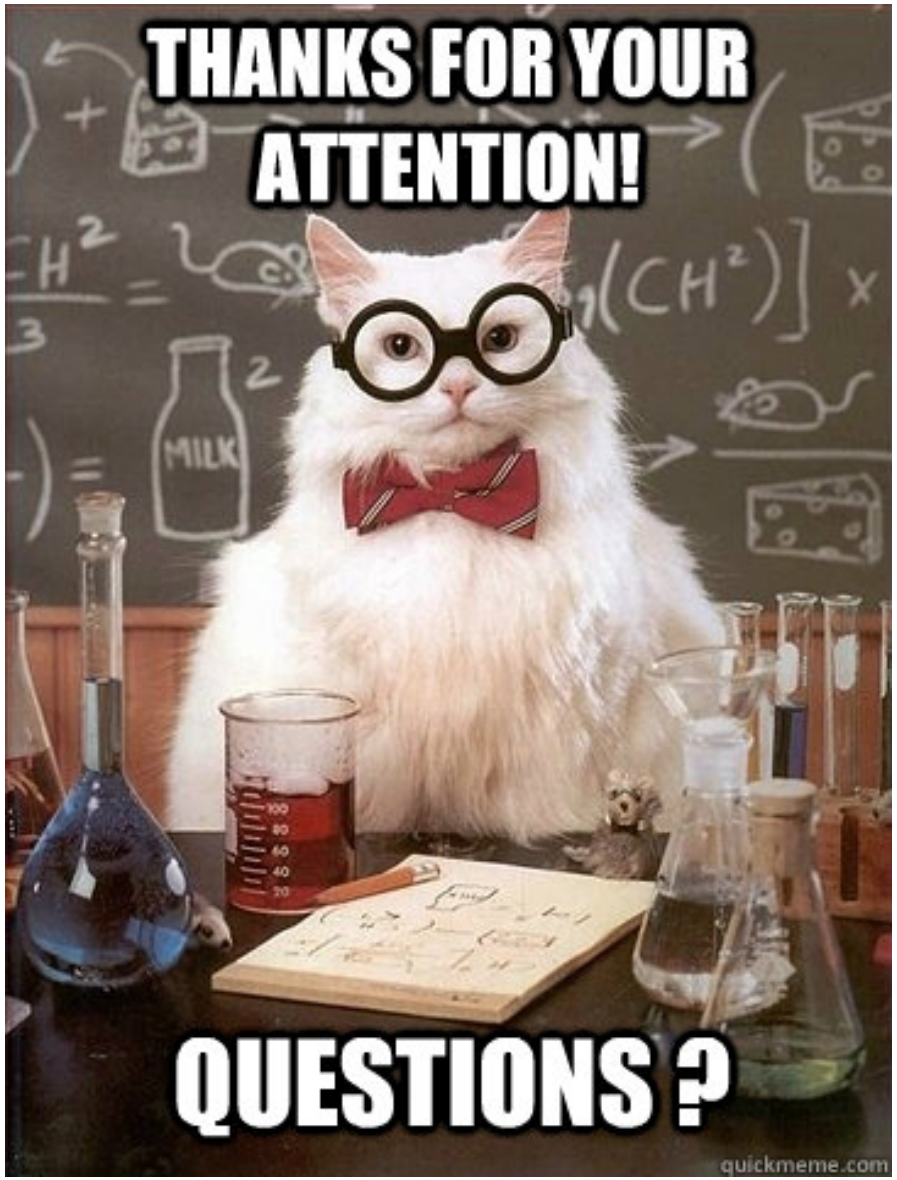
Issues of interest

- What factors predict weight loss with antiobesity drugs ?
- How effective are antiobesity drugs beyond 1 year ?
- What happens when an antiobesity drug is stopped ?

Clin Chem 2018;64(1):118-29.

Conclusion

- Chronic disease
- Differences in criteria between Thai and Western
- Negative consequences – morbidity and mortality
- Nonpharmacological is the mainstay of management
- Pharmacological is adjunctive for who fail nonpharmacological or have comorbidities
- Individualized, consider patient desires, age, degree and duration of obesity, and comorbidities
- Lifelong management
- Multidisciplinary approach



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