Hot issue :치료 패러다임 변화

비 만

인제의대 해운대백병원

김 태 년

Obesity

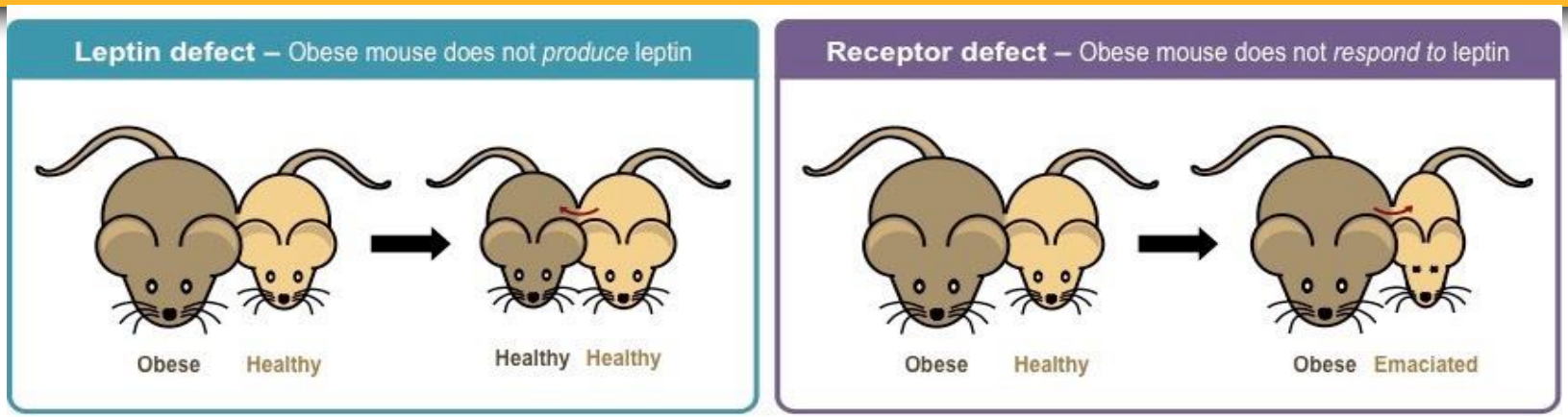
World Health Organization

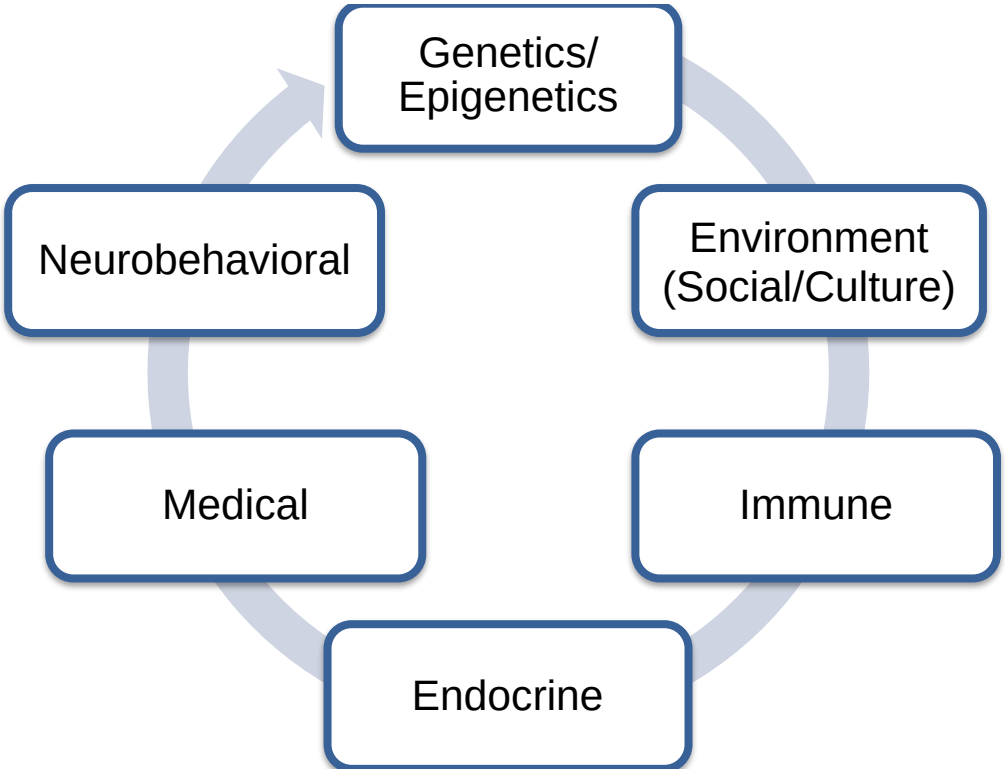
Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health.

A crude population measure of obesity is the body mass index (BMI), a person's weight (in kilograms) divided by the square of his or her height (in metres).

The WHO Consultation on Obesity met in Geneva from 3 to 5 June. 1997

Obesity as a Multifactorial Disease





Obesity Medicine Association
CLINICAL LEADERS IN OBESITY MEDICINE®

Obesity Pathogenesis:

An Endocrine Society Scientific Statement

Michael W. Schwartz, Randy J. Seeley, Lori M. Zeltser, Adam Drewnowski, Eric Ravussin, Leanne M. Redman, and Rudolph L. Leibe

"Growing evidence suggests that obesity is a disorder of the energy homeostasis system, rather than simply arising from the passive accumulation of excess weight"

Endocrine Reviews 38: 267 – 296, 2017

Related Commentary, page 22 Research article

Obesity is associated with hypothalamic injury in rodents and humans

Joshua P. Thaler,[1,2] Chun-Xia Yi,[3] Ellen A. Schur,[2] Stephan J. Guyenet,[1,2] Bang H. Hwang,[1,2,4] Marcelo O. Dietrich,[5] Xiaolin Zhao,[1,2,6] David A. Sarruf,[1,2] Vitaly Izgur,[7] Kenneth R. Maravilla,[7] Hong T. Nguyen,[1,2] Jonathan D. Fischer,[1,2] Miles E. Matsen,[1,2] Brent E. Wisse,[1,2] Gregory J. Morton,[1,2] Tamas L. Horvath,[5,8] Denis G. Baskin,[1,2,4] Matthias H. Tschöp,[3] and Michael W. Schwartz[1,2]

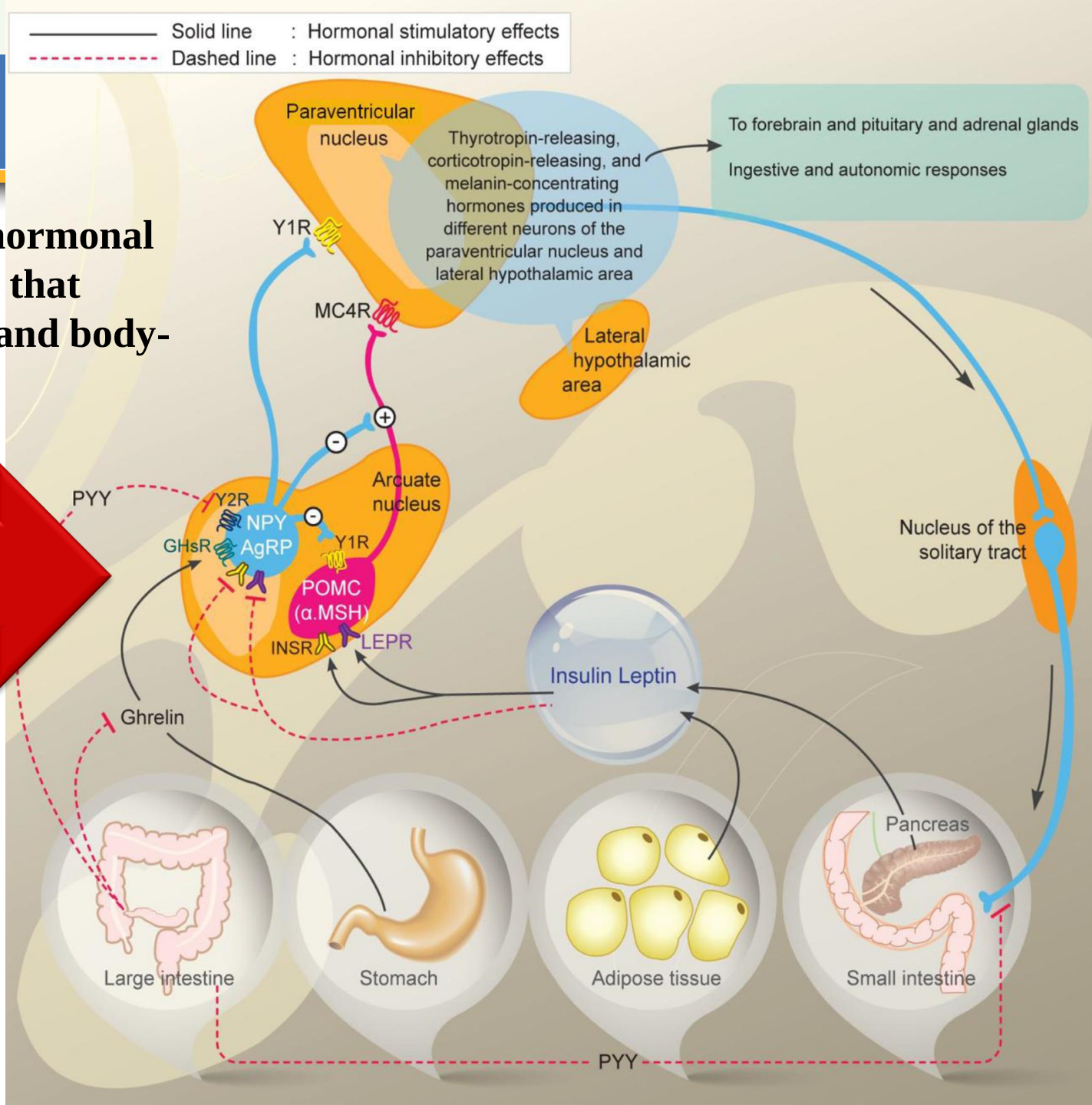
[1]Division of Metabolism, Endocrinology and Nutrition, Diabetes and Obesity Center of Excellence, and [2]Department of Medicine, University of Washington, Seattle, Washington, USA. [3]Metabolic Diseases Institute, Division of Endocrinology, Department of Medicine, University of Cincinnati, Cincinnati, Ohio, USA. [4]Research and Development Service, Department of Veterans Affairs Puget Sound Health Care System, Seattle, Washington, USA. [5]Program in Integrative Cell Signaling and Neurobiology of Metabolism, Section of Comparative Medicine, Yale University School of Medicine, New Haven, Connecticut, USA. [6]Department of Physiology and Pathophysiology, School of Medicine at Xi'an Jiaotong University, Xi'an, China. [7]Department of Radiology, University of Washington, Seattle, Washington, USA. [8]Department of Obstetrics/Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut, USA.

Rodent models of obesity induced by consuming high-fat diet (HFD) are characterized by inflammation both in peripheral tissues and in hypothalamic areas critical for energy homeostasis. Here we report that unlike inflammation in peripheral tissues, which develops as a consequence of obesity, hypothalamic inflammatory signaling was evident in both rats and mice within 1 to 3 days of HFD onset, prior to substantial weight gain. Furthermore, both reactive gliosis and markers suggestive of neuron injury were evident in the hypothalamic arcuate nucleus of rats and mice within the first week of HFD feeding. Although these responses temporarily subsided, suggesting that neuroprotective mechanisms may initially limit the damage, with continued HFD feeding, inflammation and gliosis returned permanently to the mediobasal hypothalamus. Consistent with these data in rodents, we found evidence of increased gliosis in the mediobasal hypothalamus of obese humans, as assessed by MRI. These findings collectively suggest that, in both humans and rodent models, obesity is associated with neuronal injury in a brain area crucial for body weight control.

J Clin Invest. **2012;122(1):153–162**

Interactions among hormonal and neural pathways that regulate food intake and body-fat mass.

Hypothalamic Injury

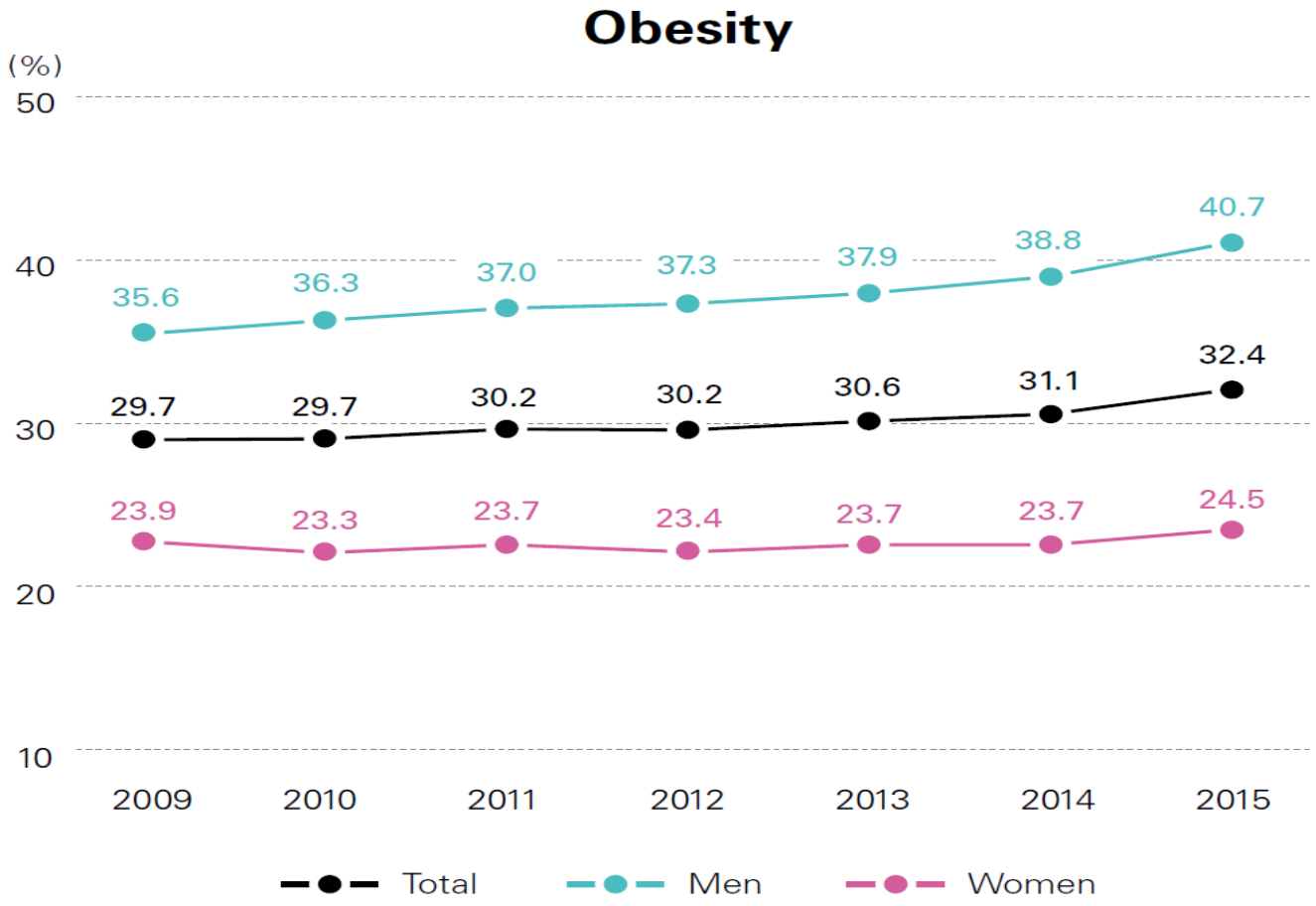


J Clin Endocrinol Metab, 2015,100(2):342–362

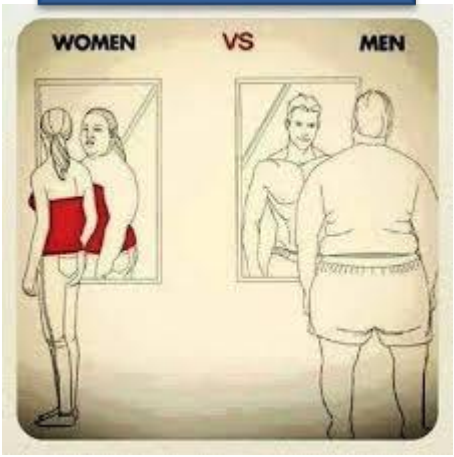
한국인에서 체질량지수와 허리둘레에 따른 비만 기준 및 동반질환 위험도

분류	체질량지수 kg/m^2	허리둘레에 따른 동반질환의 위험도	
		< 90 cm (남자), < 85 cm (여자)	≥ 90 cm (남자), ≥ 85 cm (여자)
저체중	<18.5	낮다	보통
정상	18.5~22.9	보통	증가
위험체중	23~24.9	증가	중등도
1단계비만	25~29.9	중등도	고도
2단계비만	≥30	고도	매우 고도

The prevalence of obesity



See themselves in mirror



- Data derived from the NHIS data set: 2009-2015
- Data was presented by age and sex standardization using the 2010 Census Korean population.
- The definition of obesity is a BMI ≥ 25 kg/m^2

2017 Obesity fact sheet

Case 1

- 48세/남
- 체중증가 (6 kg/1 year)
- 2형 당뇨병 (유병기간: 4년)

  F/H: none
- HbA1c: 7.2%, BMI: 29.4 kg/m^2 (85 kg, 170 cm)

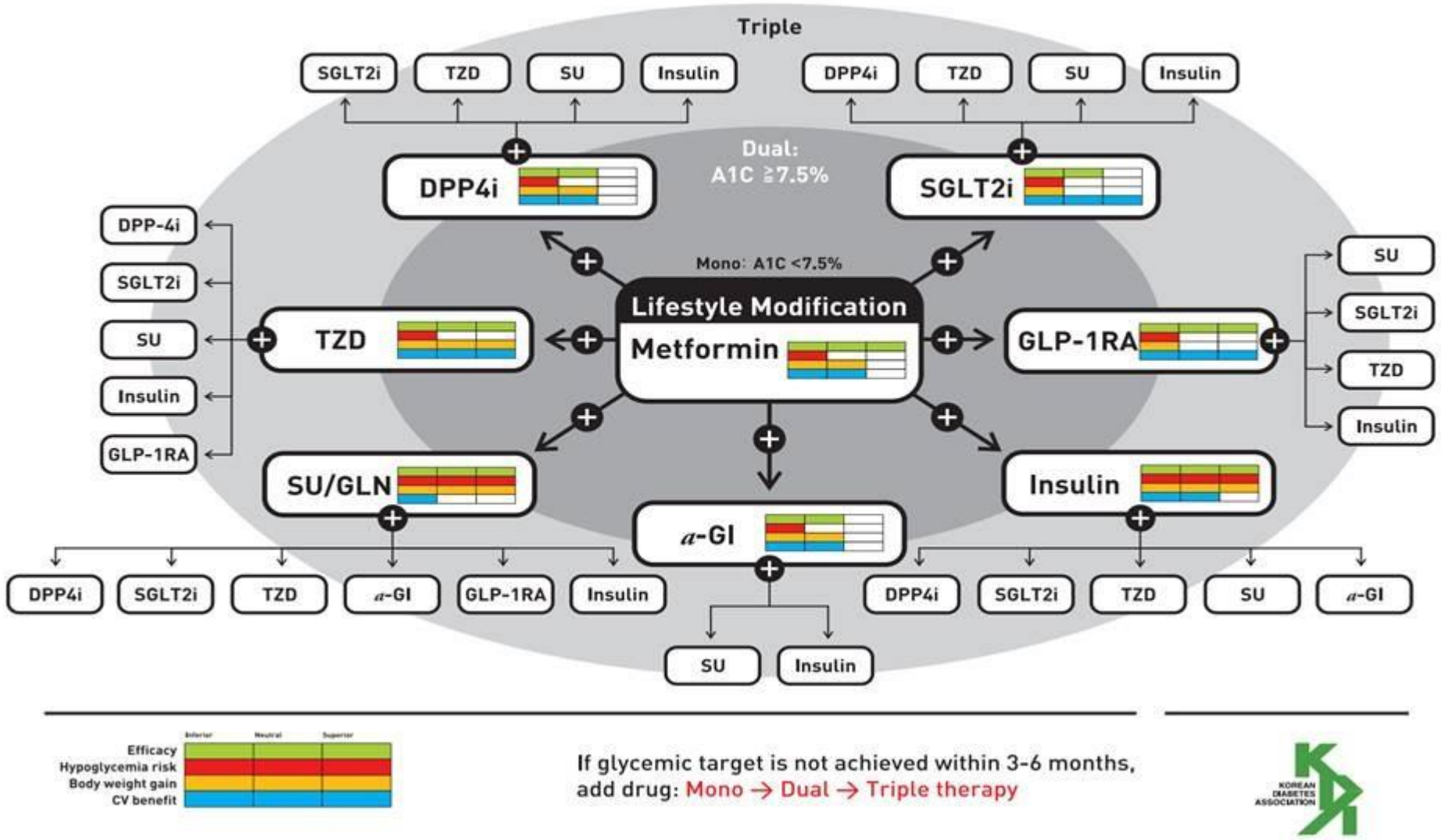
- His Medications

: pioglitazone 30 mg 1T qd
gliclazide MR 30 mg 1T qd
metformin 500 mg 1T qd
Telmisartan 80 mg 1T qd
Fenofibrate/simvastatin 160/20 mg
pregabalin 150 mg bid

Identify and Manage Concomitant Pharmacotherapy That Might Alter Body Weight

Category	Drug Class	Weight Gain	Alternatives
Psychiatric agents	Antipsychotic	Clozapine, risperidone, olanzapine, quetiapine, haloperidol, perphenazine	Ziprasidone, aripiprazole
	Antidepressants/mood stabilizers: tricyclic antidepressants	Amytriptyline, doxepin, imipramine, nortriptyline, trimipramine, mirtazapine	Bupropion[a], nefazodone, fluoxetine (short term), sertraline (<1 year)
	Antidepressants/mood stabilizers: SSRIs	Fluoxetine?, sertraline?, paroxetine, fluvoxamine	
	Antidepressants/mood stabilizers: MAOIs	Phenylzine, tranylcypromine	
	Lithium	—	
Neurologic agents	Anticonvulsants	Carbamazepine, gabapentin, valproate	Lamotrigine?, topiramate[a], zonisamide[a]
Endocrinologic agents	Diabetes drugs	Insulin (weight gain differs with type and regimen used), sulfonylureas, thiazolidinediones, sitagliptin?, metiglinide	Metformin[a], acarbose[a], miglitol[a], pramlintide[a], edenatide[a], liraglutide[a]

2017년 대한당뇨병학회 진료지침



1. SH Ko *et al*. Diabetes Metab J 2017;41337-348

Case 1

- 48세/남

- His Medications

: ~~pioglitazone 30 mg 1T qd~~
~~gliclazide MR 30 mg 1T qd~~
~~metformin 500 mg 1T qd~~
Telmisartan 80 mg 1T qd
Fenofibrate/simvastatin 160/20 mg
~~pregabalin 150 mg bid~~

Rx

Low glycemic index diet

d/c pioglitazone

gliclazide

Empagliflozine 10 mg

Metformin 1000 mg 1T bid

3 kg weight reduction

HbA1c: 7.2 → 6.6%,
BMI: 29.4 → 28.4 kg/m^2

Case 2

- 52세/남
- 살도 빼고 술도 끊고 싶다.
- 비만

  BMI: 32.4 kg/m^2

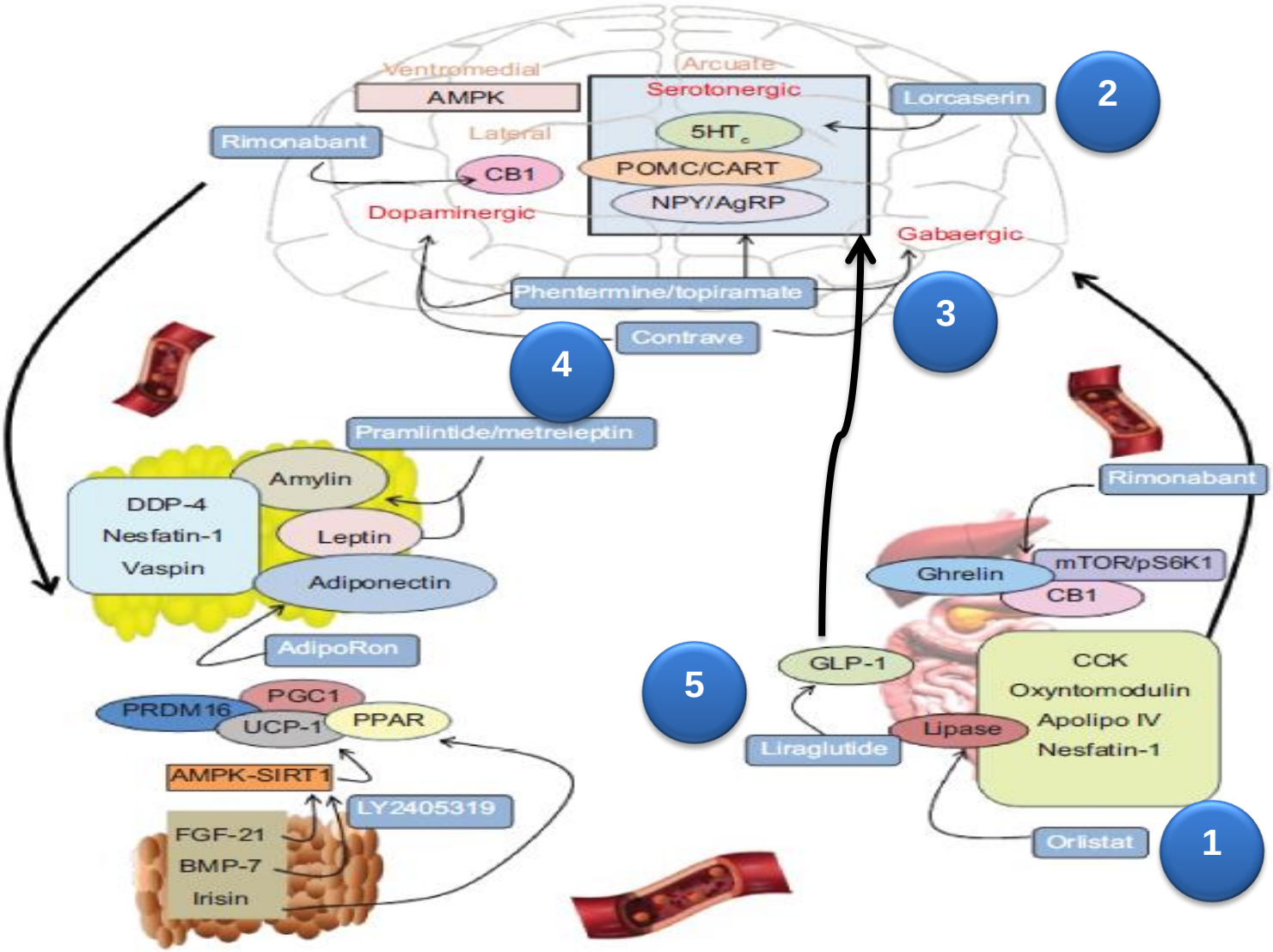
- 사업, 매일 음주(회식과 습관)
- P/Hx: 췌장염, 요로결석

A. Lorcaserin
B. Naltrexone/bupropion
C. Liraglutide 3 mg
D. Phentermine/topiramate ER
E. Bariatric surgery

Pharmacotherapy (Available for chronic use)

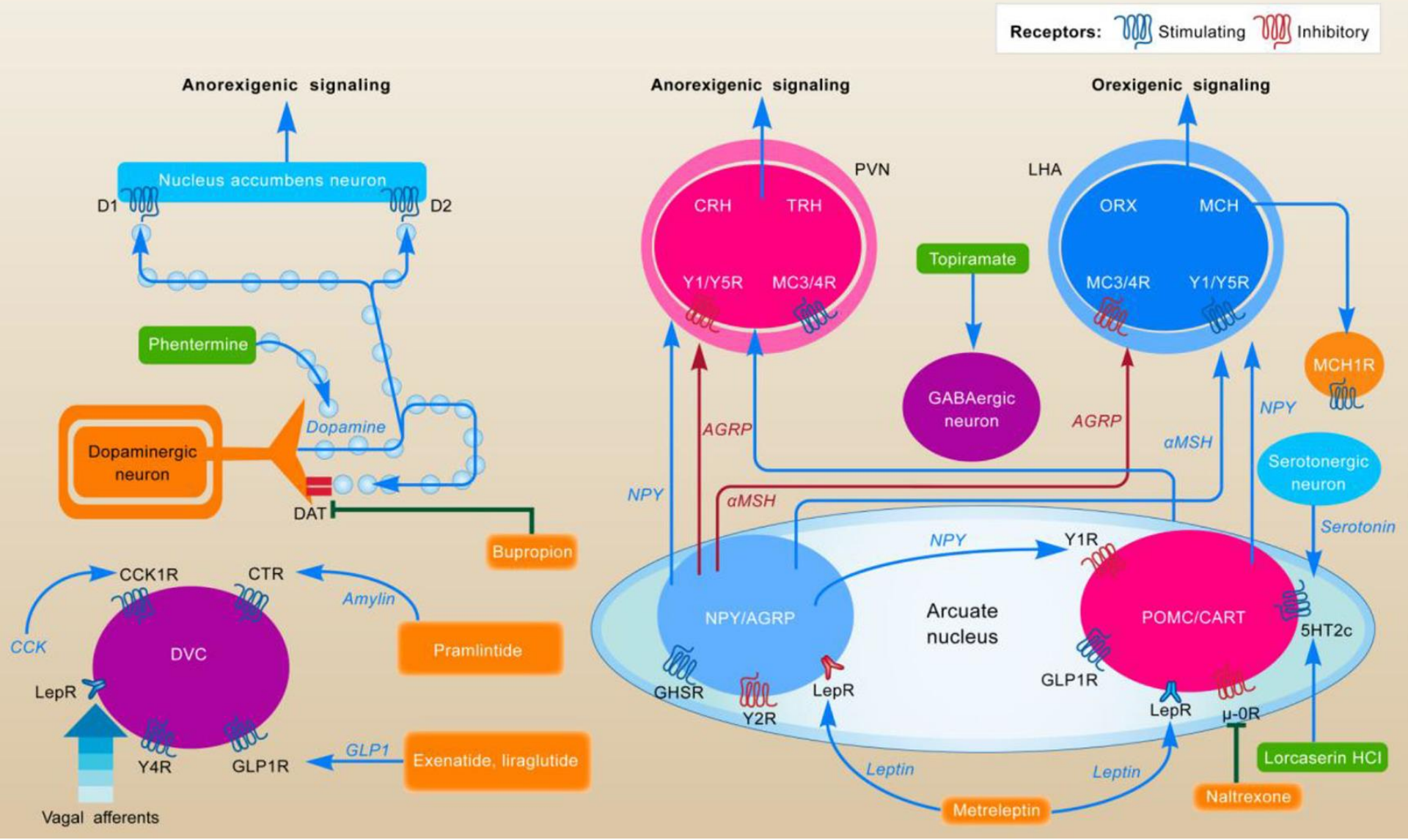
- **Orlistat (Xenical®)**
  : approval by FDA (1999)
- **Lorcaserin (Belviq®)**
  : approval by FDA (2012)
- **Phentermine/Topiramate (Qsymia®)**
  : approval by FDA (2012)
- **Naltrexone/Bupropion (Contrave® , Mysimba®)**
  : approval by FDA(2014.9), EMA (2015)
- **Liraglutide 3.0mg (Saxenda®)**
  : approval by FDA (2014), EMA (2015)

Antiobesity Agents and Their Mechanism of Action-1



Drug Design, Development and Therapy 2014:8 2391–2400

Antiobesity Agents and Their Mechanism of Action-2



J Clin Endocrinol Metab 100: 342–362, 2015

Orlistat

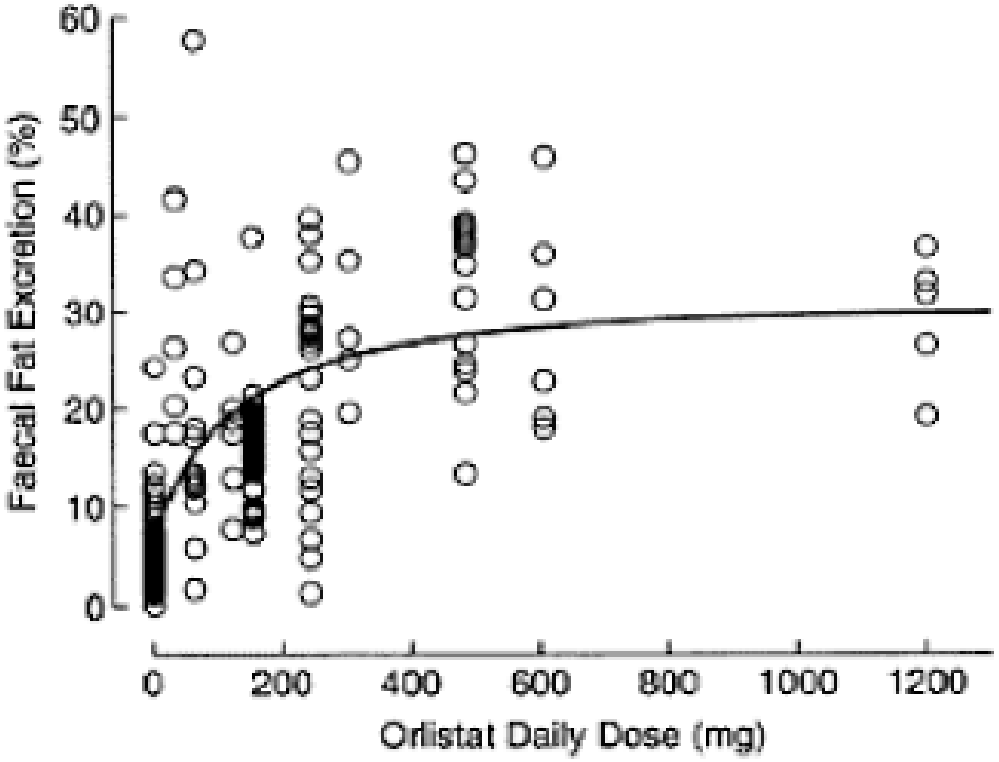
- Approved by the FDA in 1999 for the treatment of obesity

- **Gastric- and pancreatic-lipase inhibitor**
→ inactivates gastrointestinal lipase, **reducing the absorption of dietary fat**
→ daily multivitamins are often co-prescribed to prevent fat-soluble vitamin deficiencies

- Commonly experienced gastrointestinal side-effects : diarrhea, flatulence, bloating, abdominal pain and dyspepsia

Patel D. et al. Metabolism. 2015;64(11):1376-1385
Narayanaswami V. et al. Pharmacol Ther. 2017 Feb;170:116-147

How much dietary fat is expected to be excreted stool with orlistat treatment?



1회 120 mg, 1일 3회

- Dose-response relationship for the effect of orlistat on fecal fat excretion (percent of fat intake)

From Zhi. J et al. Clin. Pharmacol/ Ther. 56,82-85,1994

Locarserin

➢ Approved by FDA in 2012, about 13 years after the approval of orlistat

➢ **Selective 5-HT_{2C} agonist**

→ activates 5-HT_{2C} receptors that are expressed on POMC neurons of arcuate nucleus resulting in **increased satiety**

➢ No increase in rate of cardiac valvulopathy found after 2 years of lorcaserin treatment

➢ Most common adverse reactions (≥5%) :

- In nondiabetic participants : headache, dizziness, fatigue, nausea, dry mouth, and constipation

Patel D. et al. Metabolism. 2015;64(11):1376-1385
Narayanaswami V. et al. Pharmacol Ther. 2017 Feb;170:116-147

Naltrexone/Bupropion

➢ Approved by the FDA in 2014 as a combination product

- 1일 1정 (naltrexone 8mg + bupropion 90mg) 복용부터 시작
- 4주에 걸쳐 다음과 같이 증량

	Morning	Evening
제 1주 : 오전 1정	●	-
제 2주 : 오전 1정, 오후 1정	●	●
제 3주 : 오전 2정, 오후 1정	● ●	●
제 4주 및 이후 : 오전 2정, 오후 2정	● ●	● ●

- 음식물과 함께 복용 권장 (고지방식이 제외)
- 유지용량 도달 후 12주 이내에 투여시점 대비 체중감량이 5% 미만인 경우 복용 중단

Patel D. et al. Metabolism. 2015;64(11):1376-1385
Narayanaswami V. et al. Pharmacol Ther. 2017 Feb;170:116-147

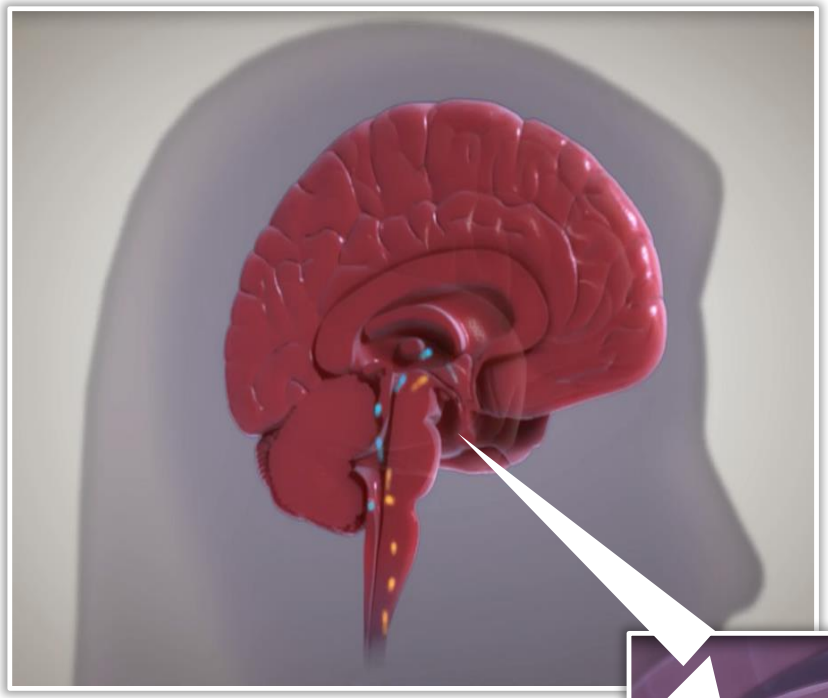
Naltrexone/Bupropion: side effects

- >10% : Nausea, constipation, headache, dizziness, vomiting
- 5-10%: Dry mouth, hot flush, insomnia, tremor, abdominal pain, tinnitus

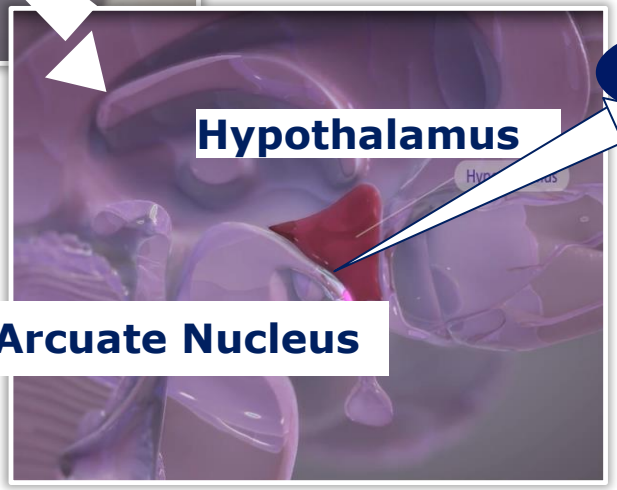
- Contraindication
  - 조절되지 않는 고혈압, 발작 병력, 양극성장애, 섭식장애, MAO 억제제 투여중인 자(투여 중지 후 최소 14일 경과 후 복용), 폐쇄각녹내장, 마약 사용자, 알코올 금단, 신장애, 중증 간장애, 임신부, 수유부, 75세 이상 고령자
  - 18세 미만, 65세 초과: 안정성 미확립
  - 뇌혈관질환 기왕력자에서 주의, 자살충동 모니터링

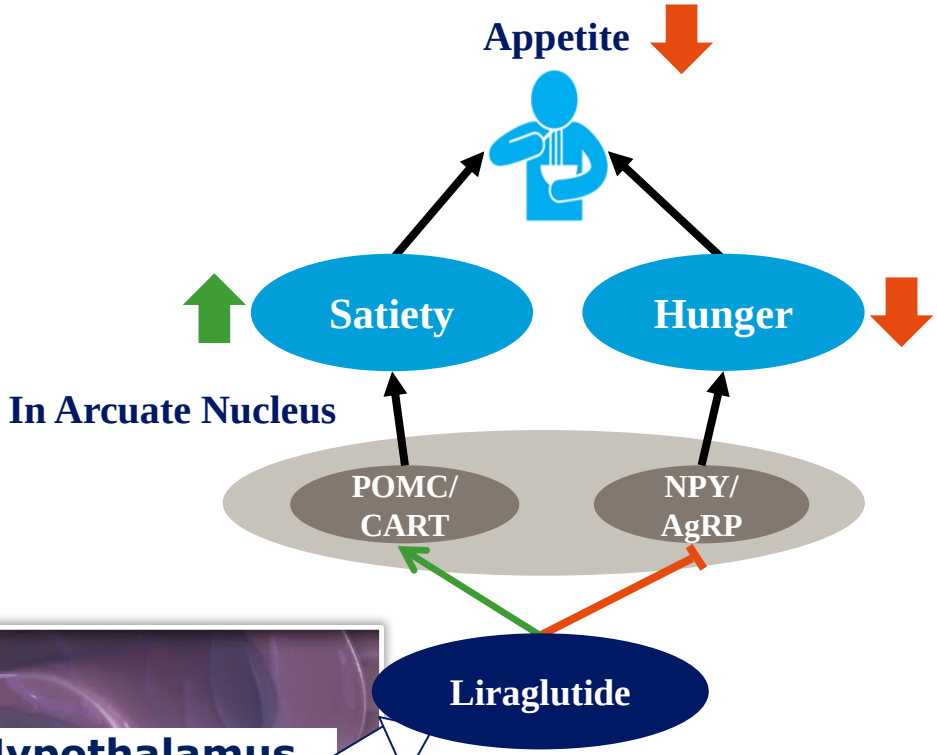
Patel D. et al. Metabolism. 2015;64(11):1376-1385
Narayanaswami V. et al. Pharmacol Ther. 2017 Feb;170:116-147

Liraglutide



Homeostatic and hedonic regulation of appetite





Metabolic effects of GLP-1

Appetite[1]

- ↑ Satiety
- ↑ Fullness
- ↓ Hunger
- ↓ Prospective food consumption
- ↓ Energy intake

Glucose regulation[2]

(Glucose-dependent)

- ↑ Insulin secretion
- ↓ Glucagon secretion

Gastric effects[3,4]

- ↓ Gastric acid
- ↓ Gastric emptying

GLP-1, glucagon-like peptide-1

1. Flint *et al. J Clin Invest* 1998;101:515–20; 2. Nauck *et al. Diabetologia* 1993;36:741–4; 3. O'Halloran *et al. J Endocrinol* 1990;126:169–73; 4. Nauck *et al. Am J Physiol* 1997;273:E981–8

liraglutide 3.0 mg (Saxenda®)

- Approved by the FDA in 2014 for chronic weight management
- **Long acting GLP-1 agonist**; **decreases appetite**
- Adverse reactions (≥5%) : nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain and increased lipase activity.

Patel D. et al. Metabolism. 2015;64(11):1376-1385
Narayanaswami V. et al. Pharmacol Ther. 2017 Feb;170:116-147

Comparison of Weight Loss and Adverse Events

Odds ratio (95% CrI) for discontinuation due to adverse events	Odds ratio (95% CrI) for achieving at least 5% weight loss					
	Phentermine-topiramate	1.67 (1.03-2.56)	2.33 (1.54-3.59)	2.98 (1.95-4.54)	3.42 (2.40-4.91)	9.22 (6.63-12.85)
0.78 (0.48-1.20)	Liraglutide	1.4 (0.96-2.18)	1.78 (1.22-2.78)	2.06 (1.51-2.96)	5.54 (4.16-7.78)	
0.87 (0.59-1.25)	1.11 (0.74-1.72)	Naltrexone-bupropion	1.28 (0.87-1.84)	1.47 (1.09-1.96)	3.96 (3.03-5.11)	
1.71 (1.14-2.49)	2.2 (1.43-3.39)	1.97 (1.38-2.76)	Lorcaserin	1.15 (0.86-1.55)	3.1 (2.38-4.05)	
1.25 (0.88-1.76)	1.6 (1.10-2.40)	1.44 (1.07-1.95)	0.73 (0.54-1.02)	Orlistat	2.7 (2.34-3.09)	
2.29 (1.71-3.06)	2.95 (2.11-4.23)	2.64 (2.1-3.35)	1.34 (1.05-1.76)	1.84 (1.53-2.21)	Placebo	

-8.8 kg -5.3 kg -5.0 kg -3.2 kg -2.6 kg

Network of Included Studies

JAMA. 2016 June 14; 315(22): 2424–2434

Case 2

- 52세/남
- 살도 빼고 술도 줄이고 싶다.
- 비만

  BMI: 32.4 kg/m^2

- 사업, 매일 음주(회식과 습관)
- P/Hx: 췌장염, 요로결석

A. Lorcaserin
B. Naltrexone/bupropion
C. Liraglutide 3 mg
D. Phentermine/topiramate ER
E. Bariatric surgery

Summary (Pharmacotherapy)

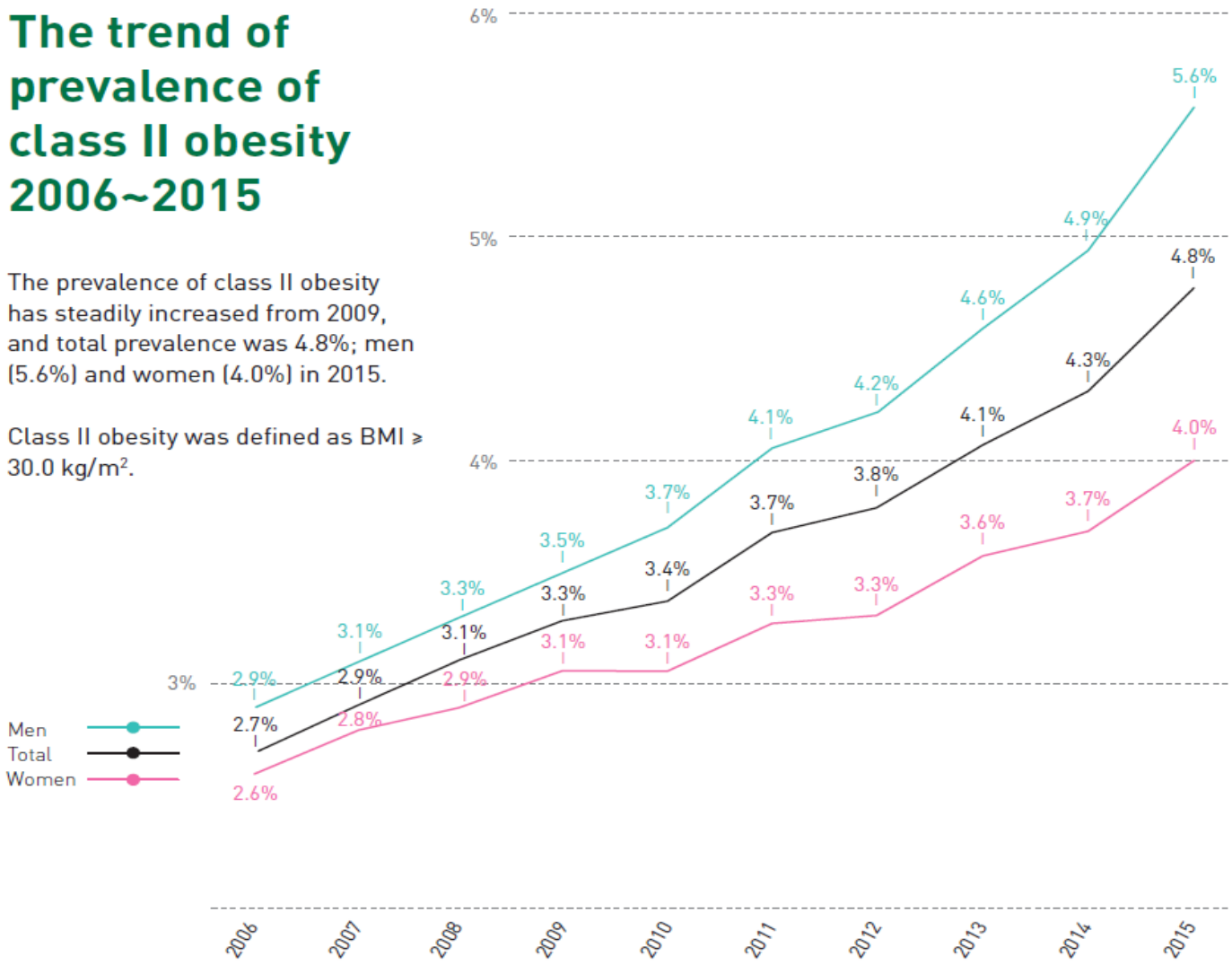
- 3개월간 비약물치료 시행: 체중의 5 % 이상 감소 실패시 시작
- 약물치료 시행 후 3개월 내에 5-10%의 체중감량이 없거나 동반 질환의 개선 효과가 보이지 않으면 약제 변경이나 중단 고려
- 아직은 naltrexone+bupropion과 Phentermine/Topiramate외 병합요법은 단일요법과 비교해서 효과보다는 부작용
- 식사치료, 운동요법, 행동요법의 **보조치료 개념으로 이해**

The prevalence of class II obesity

The trend of prevalence of class II obesity 2006~2015

The prevalence of class II obesity has steadily increased from 2009, and total prevalence was 4.8%; men (5.6%) and women (4.0%) in 2015.

Class II obesity was defined as BMI ≥ 30.0 kg/m².



2016 Obesity fact sheet

Endoscopic bariatric therapies (EBTs)

Gastric interventions

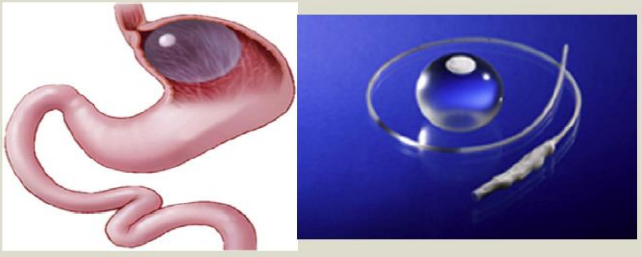
- Intragastric balloons
- Other space-occupying EBTs
- Aspiration therapy
- Gastroplasty techniques

Small-bowel interventions

- GI bypass sleeves
- Other small-bowel EBTs

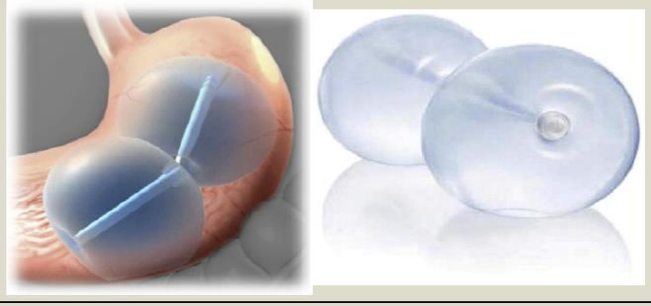
1. Intragastric balloons

Orbera
Apollo Endosurgery



Elastic spherical balloon made from silicone and filled with about 500-700 ml of saline. It is inserted and retrieved endoscopically.

ReShape Duo
ReShape Medical



Saline solution-filled, dual intragastric balloon system with 2 balloons attached to each other by a flexible tube. Each balloon has independent channels so that unintentional leaks or deflation in 1 balloon do not to impact the other balloon.

Spatz Adjustable Balloon System
Spatz Medical

Saline filled intragastric balloon with an extractable inflation tube for volume adjustment, while the IGB remains in the stomach.

Obalon Gastric Balloon
Obalon Therapeutics

Gas-filled balloon with a maximal volume of 250ml. It is compressed, folded, and fitted in a large gelatin capsule. Once the capsule is ingested, the catheter extends from the stomach to outside the body through the esophagus and the mouth. After balloon inflation, the catheter is detached and removed. One or more balloon can be swallowed during the same session.

2. Other space occupying EBTs

TransPyloric Shuttle
BAROnova, Inc.

Endoluminally delivered solid silicone funnel-type device that delays gastric emptying by intermittent sealing of pylorus with peristalsis.

Full Sense Device
BFKW LLC

Modified fully-covered gastroesophageal stent with a cylindrical esophageal component and a gastric disk that are connected by struts, which ensure that the gastric disk applies pressure on the gastric cardia to induce satiety.

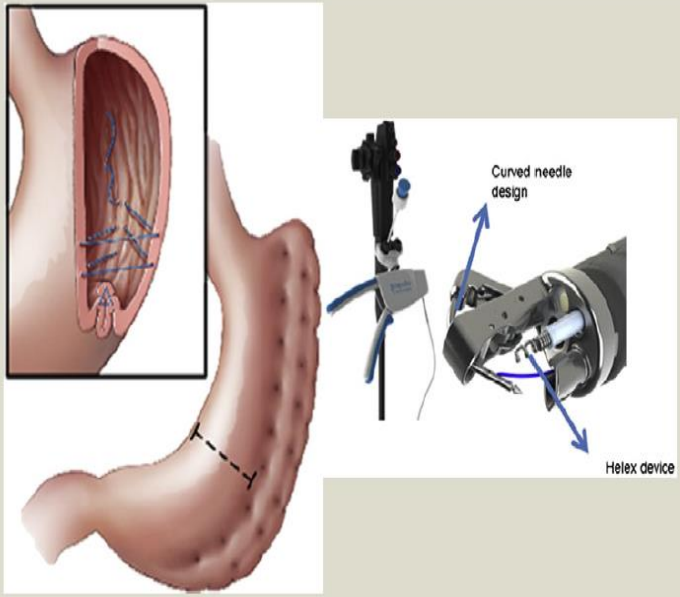
3. Aspiration Therapy

A-tube and Aspire Assist Device
Aspire Bariatrics

Specially designed percutaneous gastrostomy tube, known as the A-Tube. The tube is made of silicone and is inserted in a fashion similar to that of a percutaneous endoscopic gastrostomy tube. Two weeks after insertion, the external portion of the tube is shortened, and a connecter valve is attached. The connector valve is flush with the skin and is connected to the Aspire Assist device to allow aspiration of 30% of the ingested meal 20 minutes after ingesting it.

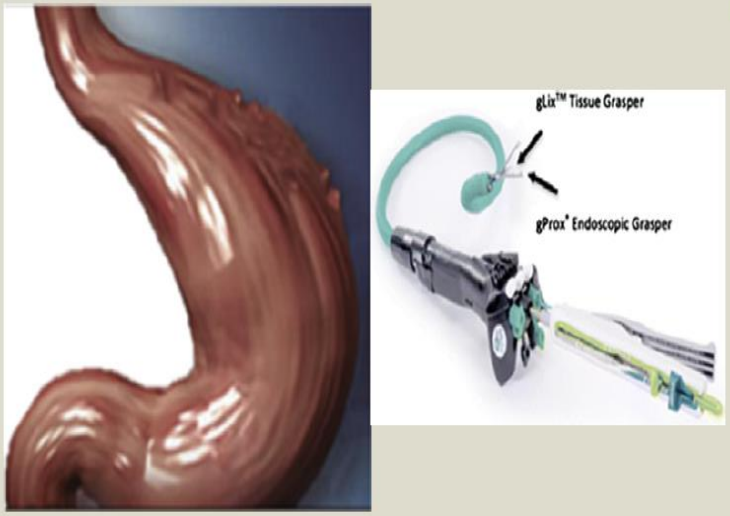
4. Gastroplasty Techniques

Endoscopic Sleeve Gastroplasty (ESG) with Overstitch Endoscopic Suturing Device
Apollo Endosurgery



ESG is created by a series of endoluminally placed free-hand, full-thickness, closely spaced sutures through the gastric wall from the pre-pyloric antrum to the gastroesophageal junction by using an endoscopic suturing device (Overstitch). This procedure reduces the entire stomach along the greater curvature, to form an endoscopically created sleeve.

Primary Obesity Surgery Endolumenal (POSE)
USGI Medical



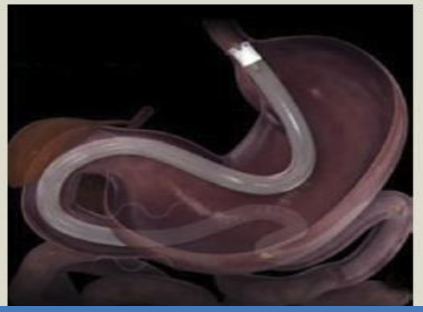
Large, overtube-style platform that has 4 working channels that can accommodate a slim endoscope and 3 specialized instruments to place transmural tissue anchor plications in the gastric fundus (to reduce accommodation) and in parts of the distal gastric body.

5. GI Bypass Sleeve

Endobarrier
GI Dynamics

Duodenaljejunal bypass sleeve made of a Teflon liner and deployed in the duodenal bulb extending 65 cm into the small bowel, creating a mechanical barrier that allows food to bypass the duodenum and proximal jejunum without mixing with pancreaticobiliary secretions until later in the gastrointestinal tract.

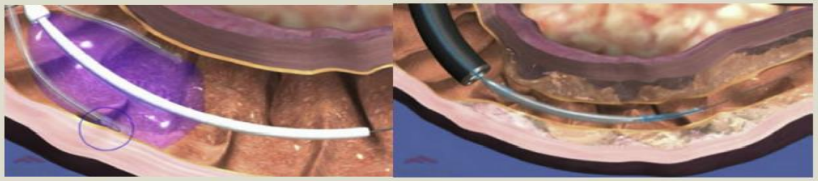
Gastroduodenojejunal Bypass Sleeve
ValenTx



120cm sleeve secured at the gastroesophageal junction, thus excluding the stomach, duodenum and proximal jejunum.

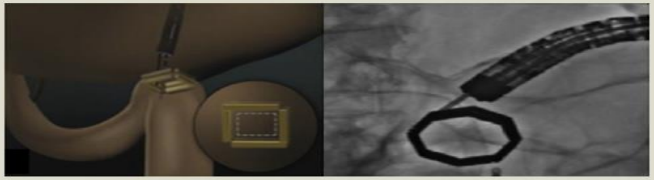
6. Other small-bowel EBTs

Duodenal Mucosal Resurfacing
Fractyl Laboratories



Specialized radiofrequency ablation technology to ablate the superficial duodenal mucosa after lifting it with a submucosal saline injection

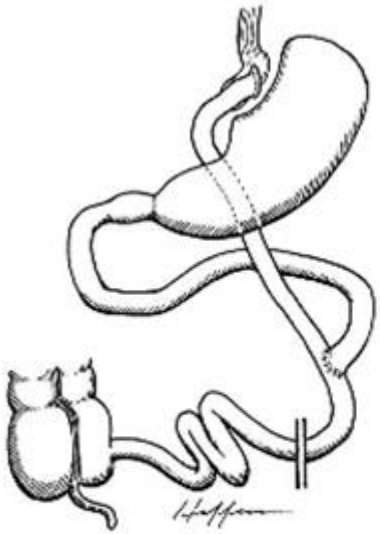
Self-assembling Magnets for Endoscopy
GI Windows



Self-assembling magnets for endoscopy is a technology that can create incisionless magnetic compression anastomoses such as gastrojejunostomies, gastroileostomies, and duodenoileostomies

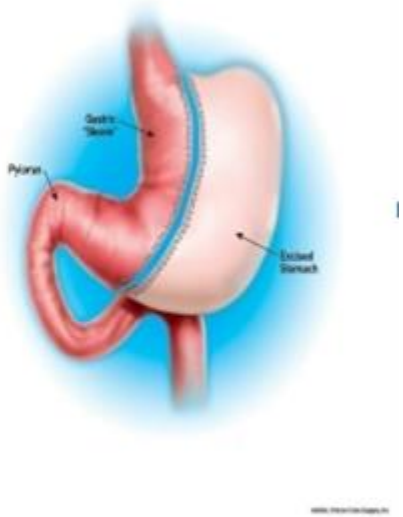
Bariatric surgery: 현재의 수술 방법

- **Restrictive procedures decrease the size of stomach to one cup**
- **Malabsorptive procedures decrease absorption of calories in the small intestine**



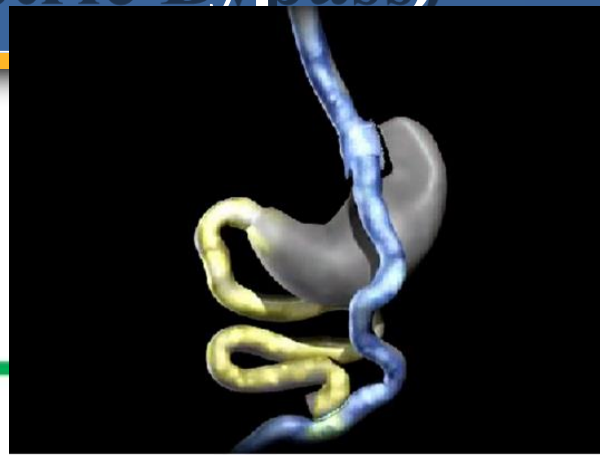
위 우회술

조절형 위밴드술

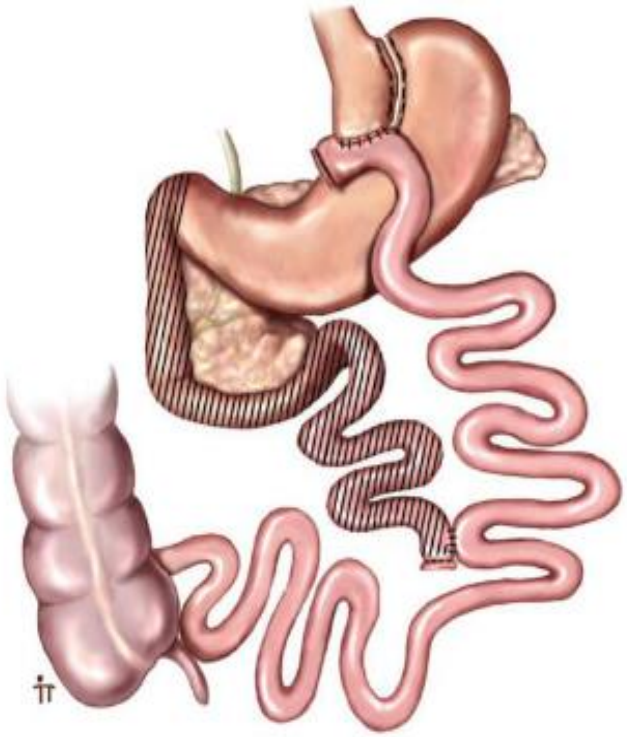


위소매절제술

복강경 위우회술 (Roux Y Gastric Bypass)



Three major components of Roux-en Y gastric bypass



- Restricted gastric volume/ excluding fundus
- Expedited access to distal jejunum and ileum
- Bypassing duodenum and upper jejunum

복강경 위우회술 (Roux Y Gastric Bypass)

- **Gold standard bariatric procedure**
- **Excellent long term weight loss**
- **Superior to purely restrictive procedures**
- **Multiple mechanisms**
  - Restriction-primary mechanism
  - Dumping (enteroglucagon)
  - Malabsorption?

Most common procedure in US

Difficult in gatric surveillance

조절형 위밴드술(Adjustable Gastric Banding)

- **Purely restrictive**
- **Adjustable stoma size via SQ port**
- **Simple, laparascopic**
- **Advantage**
  - Safe
  - Low short-term complication
- **Disadvantage**
  - Foreign body reaction
  - High long-term complication

위소매 절제술(Sleeve Gastrectomy)

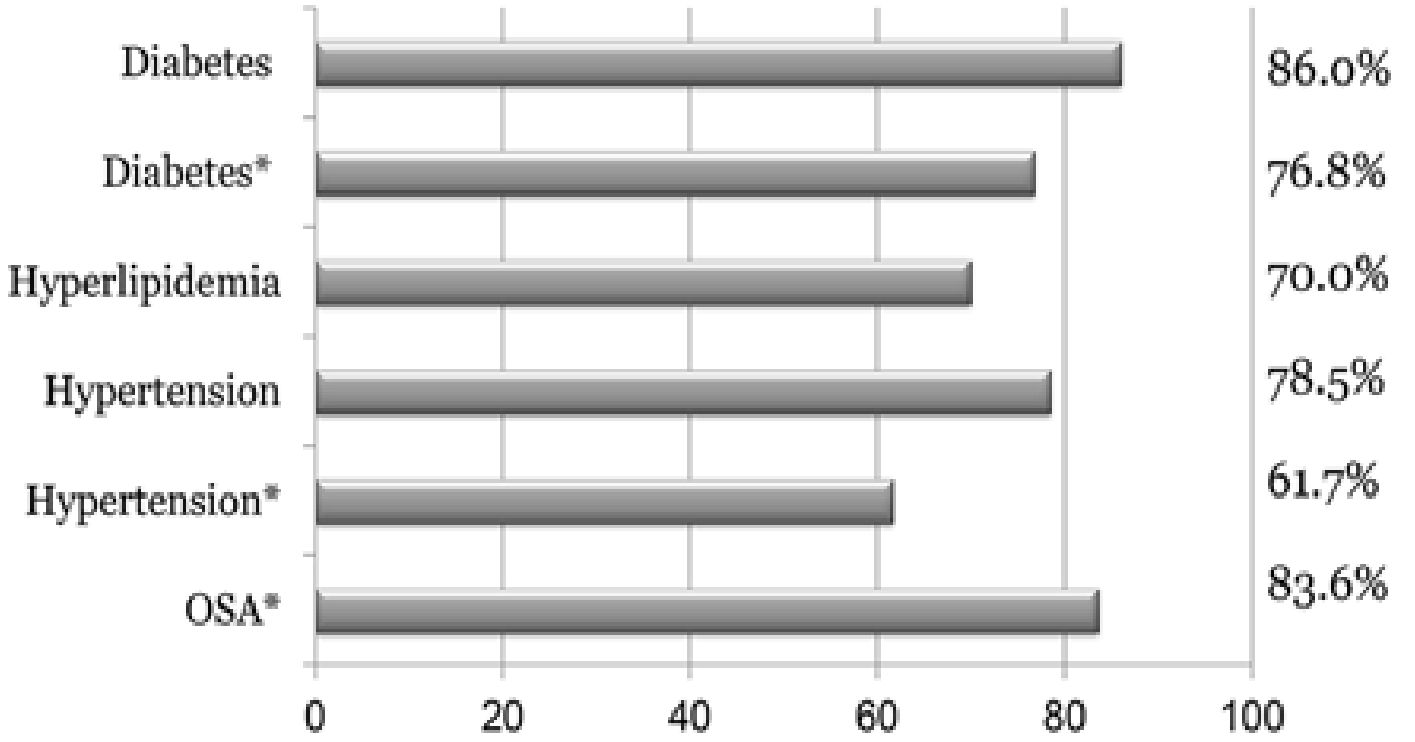
- **Primarily restrictive**
- **Additional Mechanism**
- **Less invasive than GBP**
- **More invasice than AGB**
- **Future definitive surgery**
- **Advantage**
  - Safe
  - Surveillance for gastric cancer
- **Disadvantage**
  - Permanent gastric resection
  - Gastroesophageal reflux

Typical Bariatric Surgery: Weight loss success rate

Operation name	Procedure type	Weight loss success rate (%)
Adjustible gastric banding	Pure Restrictive	50～60
Roux-en Y gastric bypass	Hybrid (restrictive & mal-absorptive)	70～80
Sleeve gastrectomy	Primarily Restrictive	60～70

The Korean Journal of Helicobacter and Upper Gastrointestinal Research, 2017;17(2):72-78
N Engl J Med 2007;357:741-52

Effects of Bariatric Surgery on Medical Complications of Obesity

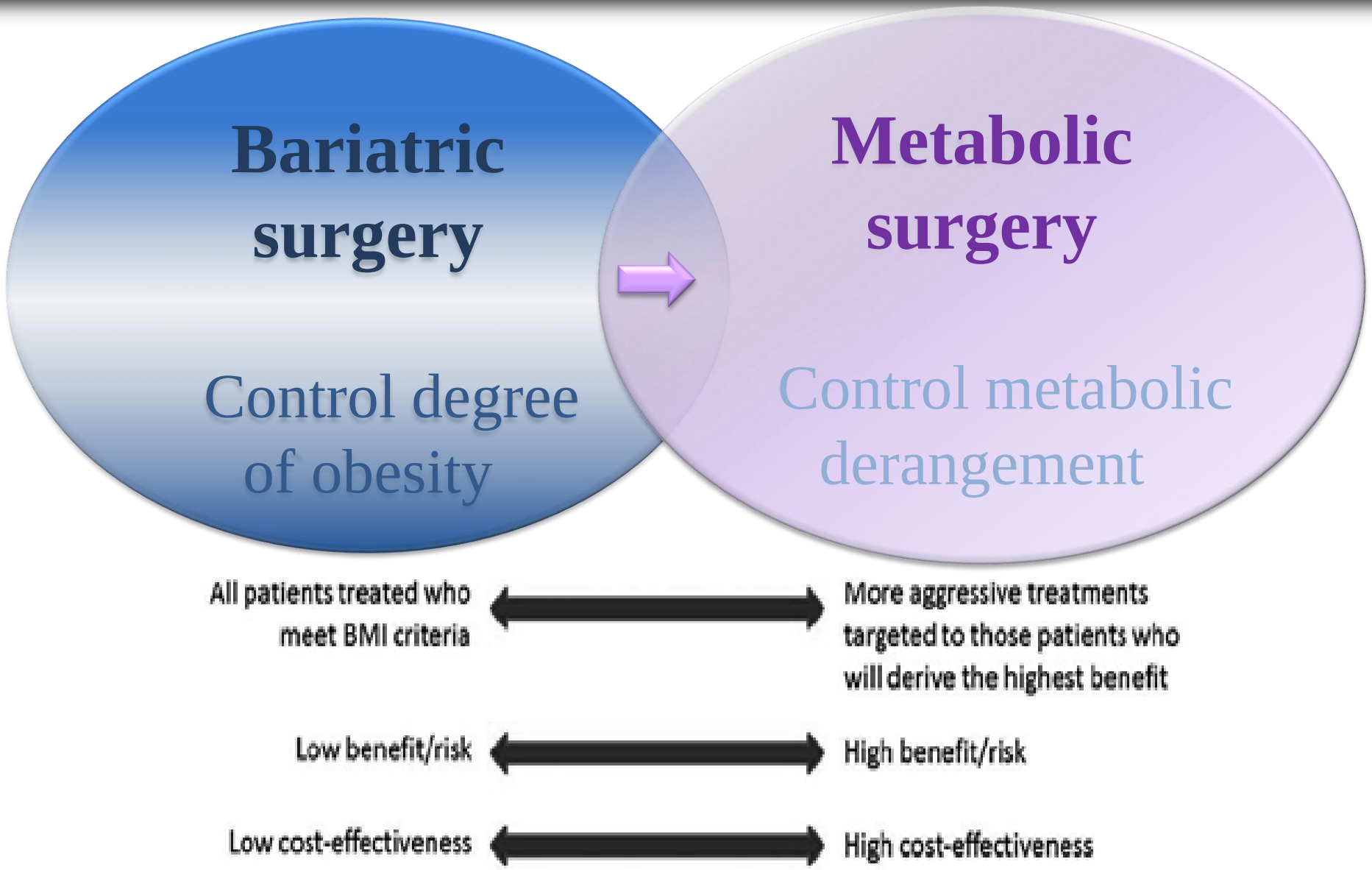


*, remission (otherwise improvement)
OSA, Obstructive sleep apnea

Bariatric surgery: a systematic review and meta-analysis

JAMA 2004;292:1724-1737

Paradigm shift: Bariatric surgery to Metabolic surgery



Conclusions

Overall Treatment Strategy

- Self-directed Lifestyle Change
- Professionally-directed Lifestyle Change
- Add Medications
- Weight Loss Surgery
- Post-surgical Combination Therapies

감 사 합 니 다