Current trend for management of obesity

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Definition of Obesity

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

WHO Classfication	BMI (kg/m^2)	BMI (kg/m^2) Korean
Underweight	<18.50	
Normal range	18.50-24.99	18.50-22.99
Overweight	≥25.00	23.00-24.99
Obese	≥30.00	≥25.00
Class I	30.00-34.99	25.00-29.99
Class II	25.00-39.99	≥30.00
Class III	≥40.00	

Prevalence of Obesity in Korea (2007-2017)

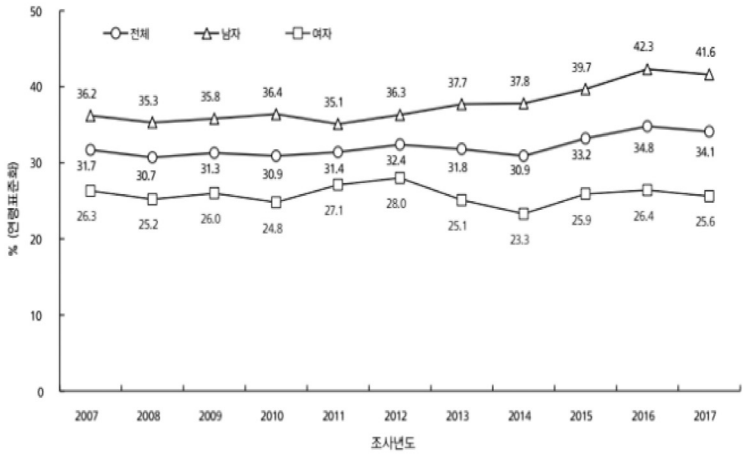
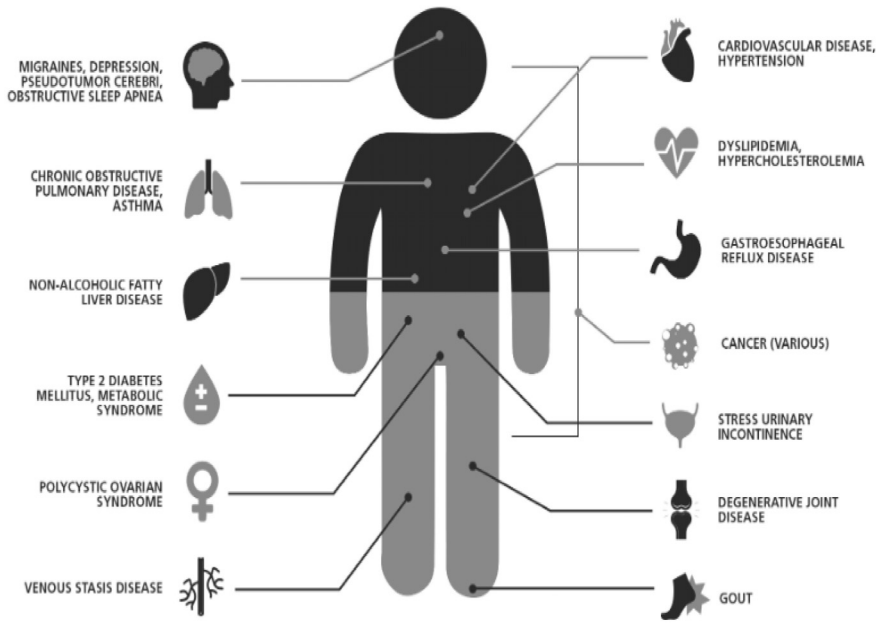


그림 1. 비만유병률 추이, 2007~2017

만 19세이상 전체 34.1%

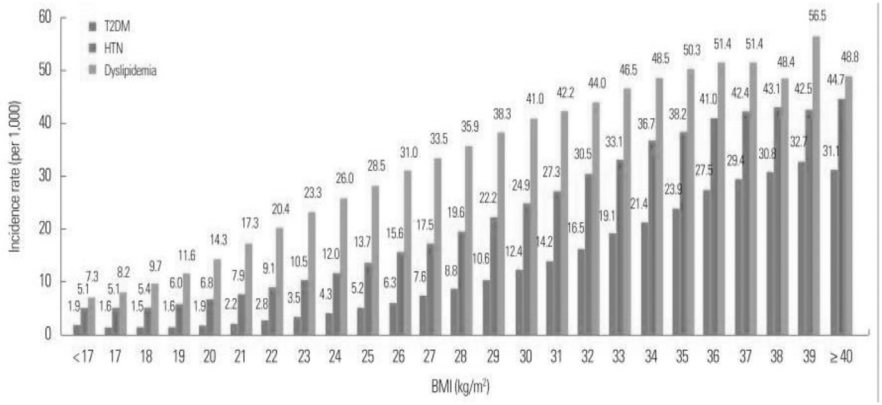
질병관리본부, 2017 국민건강통계

Complications of Obesity



Complications of Obesity

: T2DM, HTN, Dyslipidemia



National Health Insurance Service Health checkup data from 2006 to 2015

Comorbid Conditions in Obesity and Evidence for Amelioration With Weight Reduction

Comorbidity	Improvement After Weight Loss	First Author, Year (Ref)
T2DM	Yes	Cohen, 2012 (132); Mingrone, 2012 (133)[a]; Schauer, 2012 (134); Buchwald, 2009 (135)
Hypertension	Yes	Ilane-Parikka, 2008 (136); Phelan, 2007 (137); Zanella, 2006 (138)
Dyslipidemia and metabolic syndrome	Yes	Ilane-Parikka, 2008 (136); Phelan, 2007 (137); Zanella, 2006 (138)
Cardiovascular disease	Yes	Wannamethee, 2005 (139)
NAFLD	Variable outcomes	Andersen, 1991 (140); Huang, 2005 (141); Palmer, 1990 (142); Ueno, 1997 (143)
Osteoarthritis	Yes	Christensen, 2007 (144); Fransen, 2004 (145); Huang, 2000 (146); Messier, 2004 (147); van Gool, 2005 (148)
Cancer	Yes	Adams, 2009 (149); Sjöström, 2009 (150)
Major depression	Insufficient evidence	
Sleep apnea	Yes	Kuna, 2013 (151)

Abbreviation: NAFLD, nonalcoholic fatty liver disease.

[a] This study showed that weight gain within the normal-weight BMI category (ie, increase from 23 to 25 kg/m²) increased risk of T2DM 4-fold.

CM Apovian et al. JCEM, 2015,100(2): 342-362

Treatment of Obesity

- **Goals**
  - ➢ To improve the health of the patient
  - ➢ To prevent or treat weight-related complications

Lifestyle interventions
Diet, Physical activity, Behavior therapy

✓ The first line of treatment

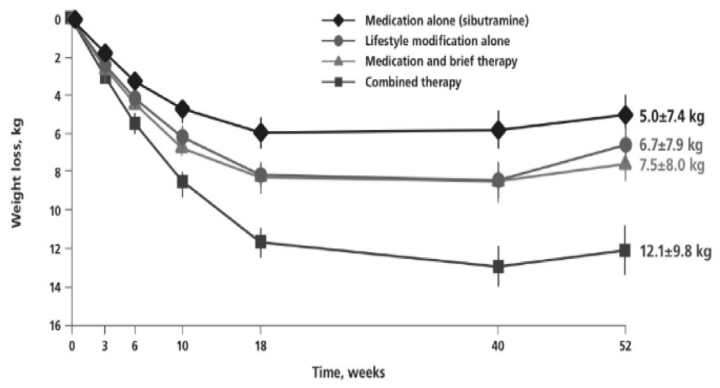
Pharmacotherapy

Bariatric surgery

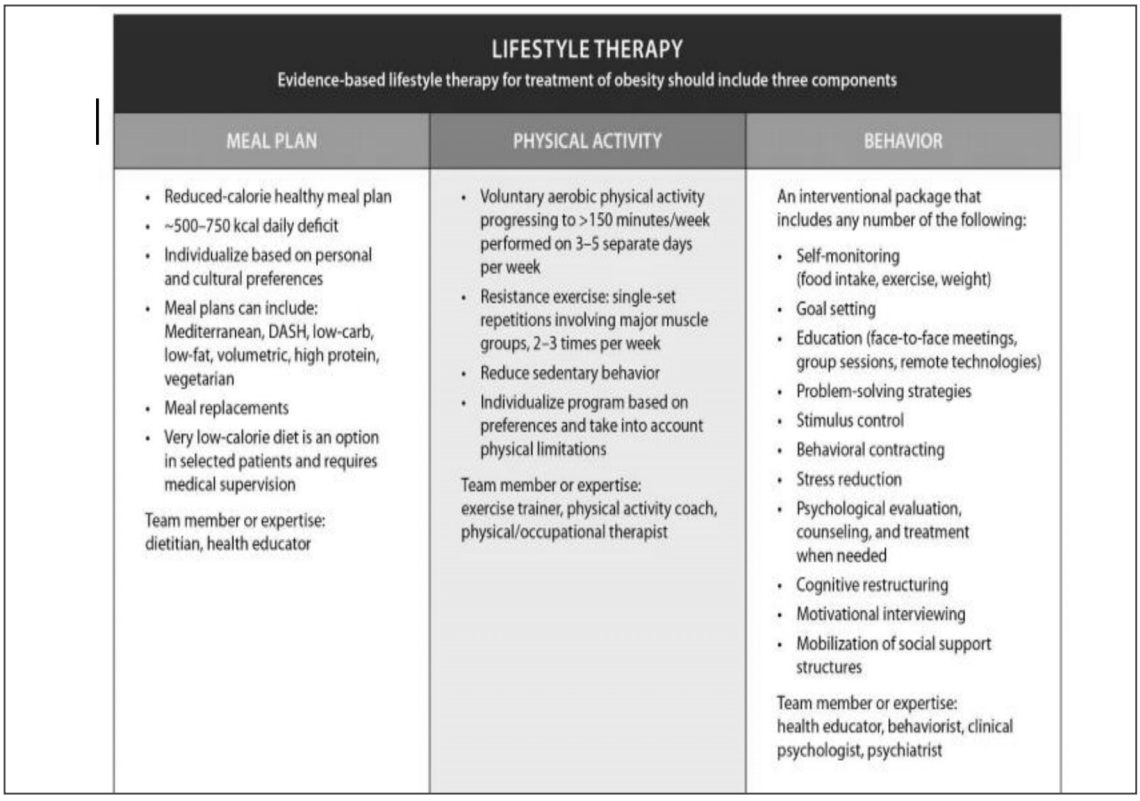
TREATMENT OF OBESITY

Treatment plans that include pharmacotherapy, as an adjunct to healthy eating and increased physical activity, may be more effective than any of those alone[4]

From a 1-year study of 224 patients with BMI of 30 to 45 kg/m^2



Wadden TA et al. NEJM. 2005;353(20): 2111-2120



LIFESTYLE THERAPY

Evidence-based lifestyle therapy for treatment of obesity should include three components

MEAL PLAN	PHYSICAL ACTIVITY	BEHAVIOR
• Reduced-calorie healthy meal plan • ~500–750 kcal daily deficit • Individualize based on personal and cultural preferences • Meal plans can include: Mediterranean, DASH, low-carb, low-fat, volumetric, high protein, vegetarian • Meal replacements • Very low-calorie diet is an option in selected patients and requires medical supervision Team member or expertise: dietitian, health educator	• Voluntary aerobic physical activity progressing to >150 minutes/week performed on 3–5 separate days per week • Resistance exercise: single-set repetitions involving major muscle groups, 2–3 times per week • Reduce sedentary behavior • Individualize program based on preferences and take into account physical limitations Team member or expertise: exercise trainer, physical activity coach, physical/occupational therapist	An interventional package that includes any number of the following: • Self-monitoring (food intake, exercise, weight) • Goal setting • Education (face-to-face meetings, group sessions, remote technologies) • Problem-solving strategies • Stimulus control • Behavioral contracting • Stress reduction • Psychological evaluation, counseling, and treatment when needed • Cognitive restructuring • Motivational interviewing • Mobilization of social support structures Team member or expertise: health educator, behaviorist, clinical psychologist, psychiatrist

Pharmacological Interventions

- **The Asia-Pacific WHO recommendations**
  - **BMI is ≥25 kg/m^2,**
  - **≥23 kg/m^2 with associated comorbidities**

    (e.g. hypertension, dyslipidemia, T2DM, OSA)

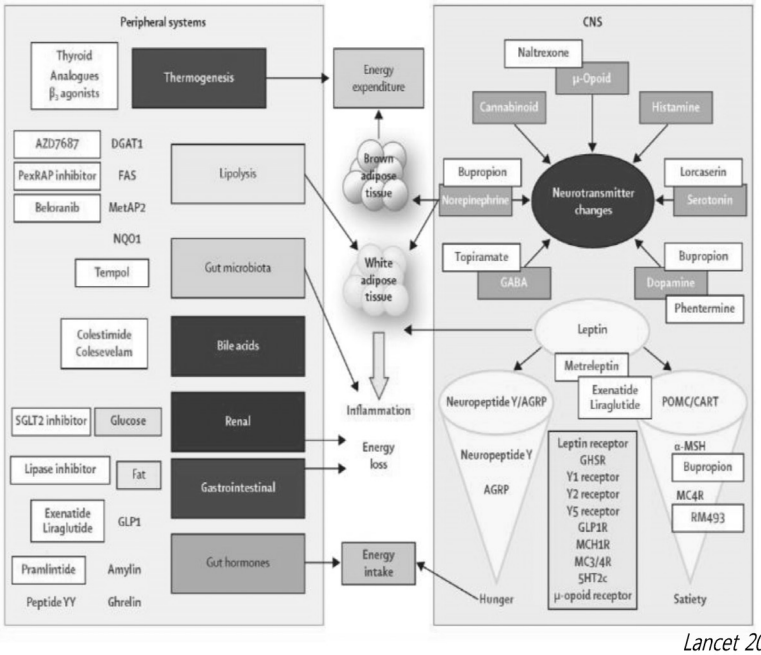
- **FDA requirements for weight management agents**
  - **There is statistically significant difference in weight loss between the intervention and placebo-treated groups (a mean absolute difference of ≥5%)**
  - **At least 35% of subjects who experience weight loss of ≥5% received the active drug.**
  - **The proportion of patients who experience weight loss in the intervention group is approximately double that in the placebo group.**

Am J Health Sys Pharm 2015; 72: 697-706

Current US FDA approved anti-obesity medications

Agents	Action	Approval
	Previously available	
Phentermine	Sympathomimetic	1959
Orlistat	GI lipase inhibitor	1997
	Recently Approved	
Phentermine/ Topiramate ER	Sympathomimetic/ Anticonvulsant (GABA receptor modulation?)	Approved, Summer 2012
Locaserin	5-HT_{2C} serotonin receptor agonist	Approved, Summer 2012
Naltrexone ER/ Bupropion ER	Dopamine noradrenaline reuptake inhibitor/ Opioid receptor antagonist	Approved, September 2014
Liraglutide 3mg	GLP-1 receptor agonist	Approved, December 2014

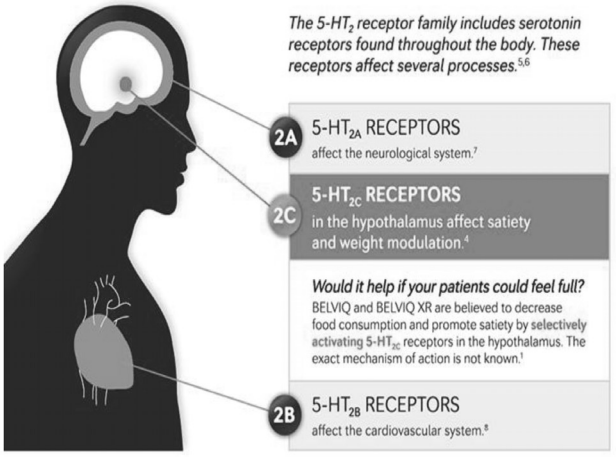
Targets of anti-obesity drugs



Lancet 2016; 387: 1947-56

Lorcaserin (Belviq®)

Specific 5-HT_{2C} receptor agonist
Dosing: 10mg twice daily

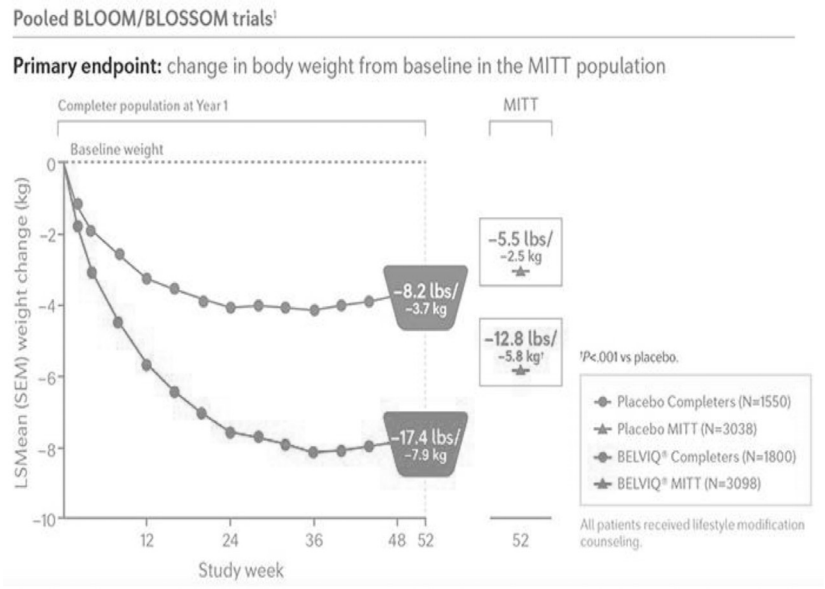


Clinical trials of Lorcaserin

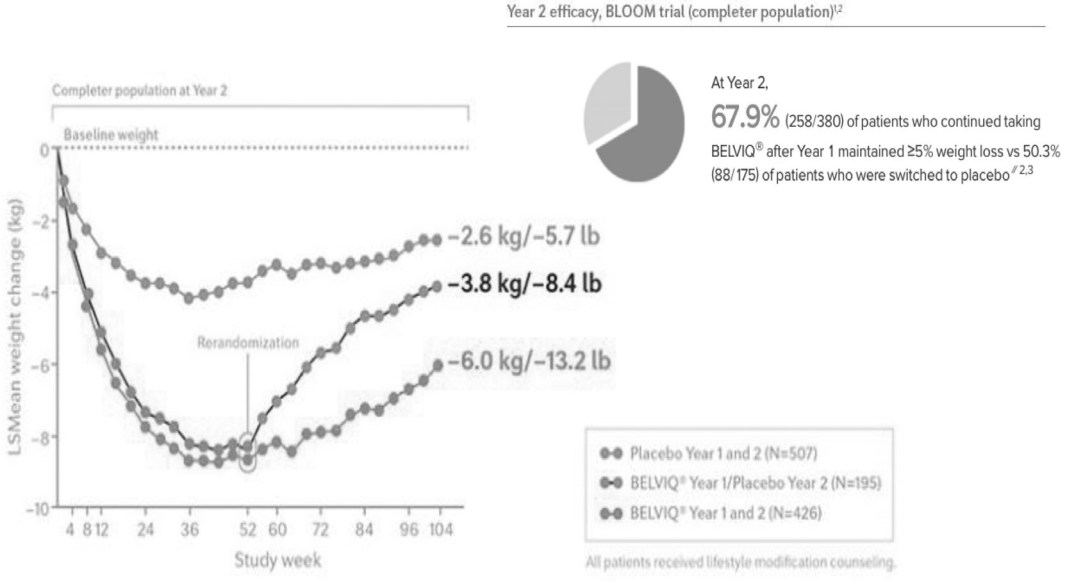
- **BLOOM** : Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management *(NEJM 2010; 363(3): 245-256)*
- **BLOSSOM** : A One-year Randomized Trial of Lorcaserin for Weight Loss in Obese and Overweight Adults *(JCEM 2011; 96(10): 3067-3077)*
- **BLOOM-DM** : Randomized Placebo-Controlled Trial of Lorcaserin for Weight Loss in Type 2 Diabetes Mellitus *(Obesity 2012; 20: 1426-1436)*

Title	Enrolled	Duration	Overweight adults with type2 DM
BLOOM	3,182	2 year	Excluded
BLOSSON	4,008	1 year	Excluded
BLOON-DM	604	1 year	Included

Effect of Locaserin on Body weight



Effect of Locaserin on Body weight



Effect of Lorcaserin on Cardiometabolic Risk Markers

	Risk Factors	Lorcaserin 10mg		P value
BLOOM study	Systolic BP, mmHg	↓	-1.4	0.04
	Diastolic BP, mmHg	↓	-1.1	0.01
	Triglycerides, %	↓	-6.15	<0.001
	Total cholesterol, %	↓	-0.90	0.001
	LDL-C, %	↑	2.87	0.049
	HDL-C, %	↑	0.05	NS
	hsCRP, mg/L	↓	-1.19	<0.001
	Fibrinogen, mg/dL	↓	-21.5	0.001
BLOOM-DM study	HbA1c, %	↓	-0.9	<0.001
	Fasting Glucose, mg/dL	↓	-27.4	<0.001

Adverse reactions of Lorcaserin

	Placebo (n=3,185)	BELVIQ BID (n=3,195)
Headache	10.1%	16.8%
Dizziness	3.8%	8.5%
Fatigue	3.6%	7.2%
Nausea	5.3%	8.3%
Dry mouth	2.3%	5.3%
Constipation	3.9%	5.8%

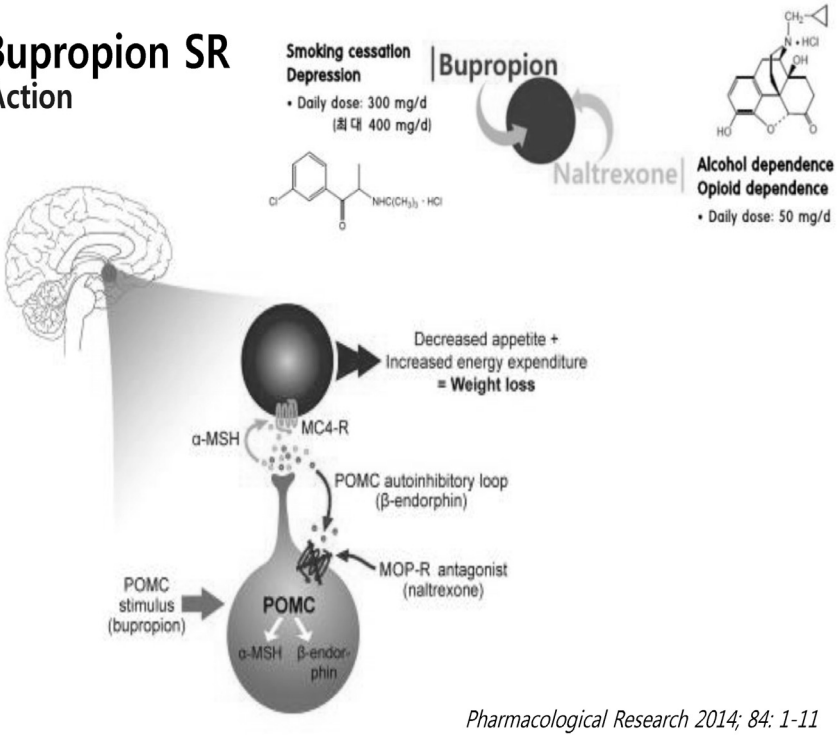
Naltrexone/Bupropion SR (Contrave®)

- Naltrexone: opioid receptor antagonist
- Bupropion: norepinephrine-dopamine inhibitor

- Dosing

	Week 1	Week 2	Week 3	Week 4 and Beyond
AM Tip: Take with breakfast	1 pill in AM	1 pill in AM	2 pills in AM	2 pills in AM
PM Tip: Take before dinner		1 pill in PM	1 pill in PM	2 pills in PM

Naltrexone/Bupropion SR
Mechanism on Action



Pharmacological Research 2014; 84: 1-11

Clinical trials of Naltrexone/Bupropion SR

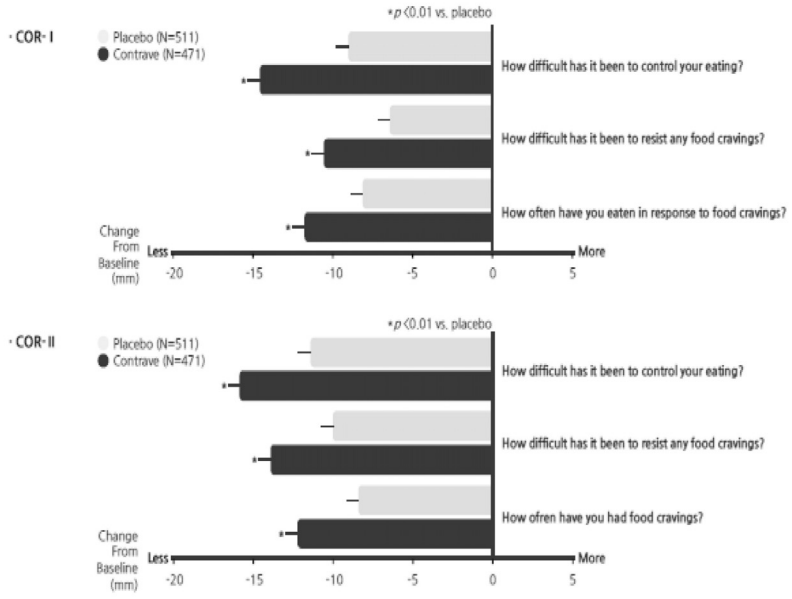
Trial	Abbreviation	Length of study (weeks)	Number of participants	Objective
Contrave Obese Research I (COR-I)	NB-301	56	1742	Compared safety and efficacy of two doses of naltrexone SR/bupropion SR in overweight and obese patients
Contrave Obese Research-Behavior Modification (COR-BMOD)	NB-302	56	793	Assessed safety and efficacy in overweight and obese patients with controlled hypertension and/or dyslipidemia with or without behavior modification
Contrave Obese Research II (COR-II)	NB-303	56	1496	Tested efficacy in overweight and obese patients with controlled hypertension and/or dyslipidemia with or without diet and exercise
Contrave Obese Research-Diabetes (COR-Diabetes)	NB-304	56	505	Determined safety and efficacy in overweight and obese patients with type 2 diabetes
Cardiovascular Outcomes Study of Contrave in Overweight and Obese Subjects With Cardiovascular Risk Factors	Light Study	Up to 4 years	Approximately 8900	Investigate cardiovascular health outcomes in overweight and obese individuals with cardiovascular risk factors. The study is designed to assess the occurrence of Major Adverse Cardiovascular Events

Effect of Naltrexone/Bupropion SR on Body weight

Table 4 Body Weight Changes at 56 Weeks in Contrave Obesity Research (COR) Clinical Trials

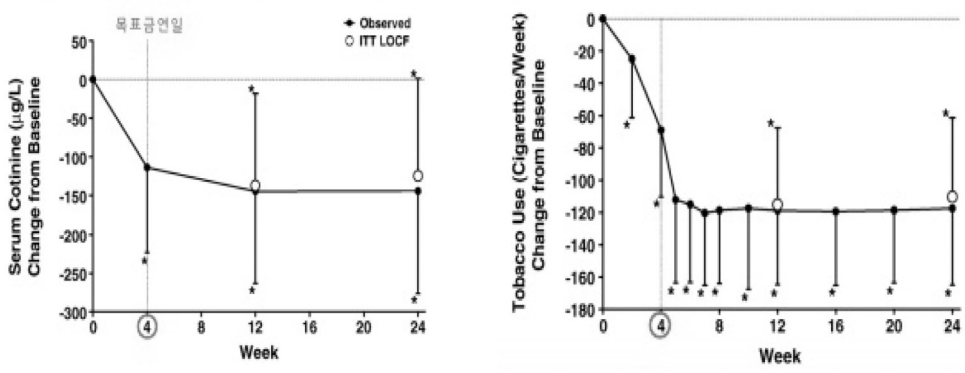
	COR-I[21]		COR-II[22,a]		COR-BMOD[23]		COR-Diabetes[24]	
	Naltrexone/ Bupropion 32/360 mg	Placebo	Naltrexone/ Bupropion 32/360 mg	Placebo	Naltrexone/ Bupropion 32/360 mg	Placebo	Naltrexone/ Bupropion 32/360 mg	Placebo
Intent-to-Treat[b]	**n = 538**	**n = 536**	**n = 820**	**n = 474**	**n = 565**	**n = 196**	**n = 321**	**n = 166**
Percent change in body weight from baseline, LS mean	−5.4%[d]	−1.3%	−5.6%[c]	−1.2%	−8.1%[c]	−4.9%	−3.7%[c]	−1.7%
Patients with ≥ 5% weight loss	42%[d]	17%	47.9%[c]	16.9%	57%[d]	43%	36%[d]	18%
Patients with ≥ 10% weight loss	21%[d]	7%	28.1%[d]	6.1%	35%[d]	21%	15%[e]	5%
Completers[c]	**n = 296**	**n = 290**	**n = 434**	**n = 267**	**n = 301**	**n = 106**	**n = 175**	**n = 100**
Percent change in body weight from baseline, LS mean	−8.1%[f]	−1.8%	−8.2%[c]	−1.4%	−11.5%[d]	−7.3%	−5.9%[c]	−2.2%
Patients with ≥ 5% weight loss	62%[f]	23%	64.9%[c]	21.7%	80.4%[c]	60.4%	53.1%[c]	24%
Patients with ≥ 10% weight loss	34%[f]	11%	39.4%[d]	7.9%	55.2%[d]	30.2%	26.3%[d]	8.0%

Effect of Naltrexone/Bupropion SR on food craving control



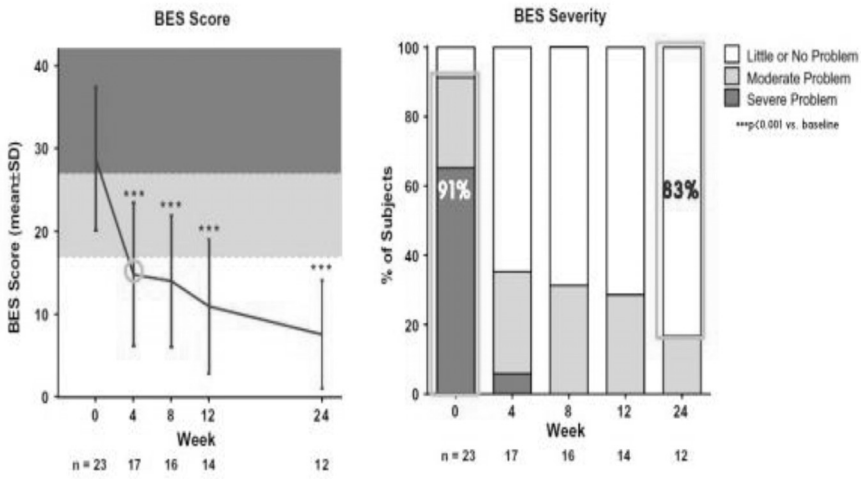
* Control of Eating Questionnaire (COEQ): 식욕, 식탐, 섭식행동 등을 측정하기 위한 도구, 자가보고식 20 visual analogue scales로 구성

Effect of Naltrexone/Bupropion SR on Tobacco Use



Charles S et al. Additive Behaviors 2010:35; 229-34

Effect of Naltrexone/Bupropion SR on Both Binge eating and Depressive Symptoms



Anna L et al. Adv Ther 2017;34: 2307-2315

Adverse reactions of Naltrexone/Bupropion SR

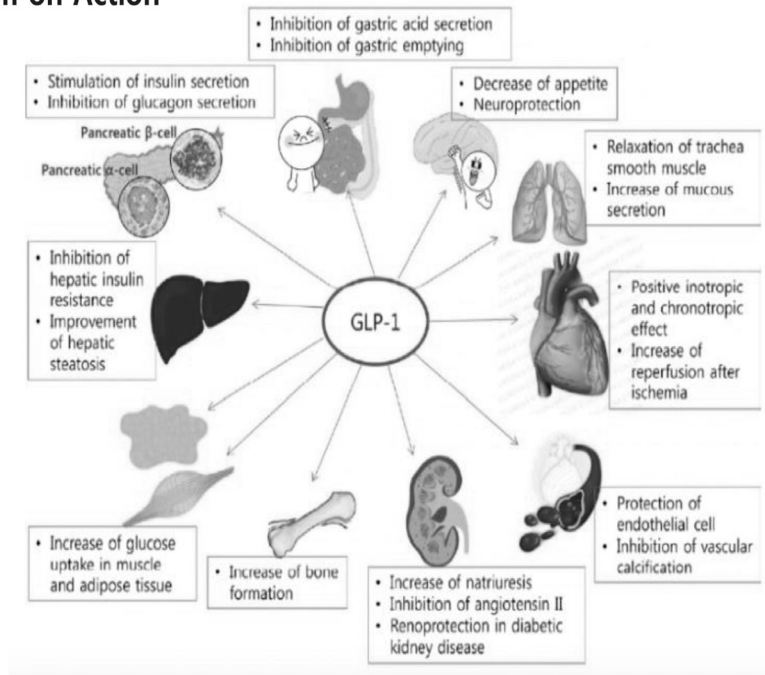
	Placebo (n=1,515)	Naltrexone/Bupropion SR 32/360mg (n=2,545)
Nausea	6.7%	32.5%
Constipation	7.2%	19.2%
Headache	10.4%	17.6%
Vomiting	2.9%	10.7%
Dizziness	3.4%	9.9%
Insomnia	5.9%	9.2%
Dry mouth	2.3%	8.1%
Diarrhea	5.2%	7.1%

Liraglutide (Saxenda®)

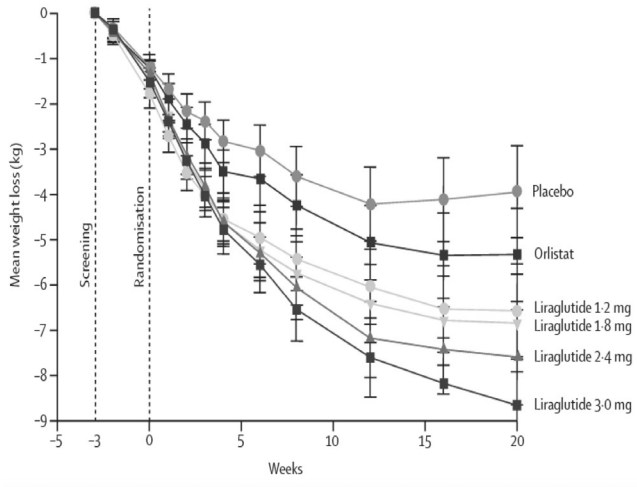
- GLP-1 receptor agonist

- Dosing

Liraglutide
Mechanism on Action



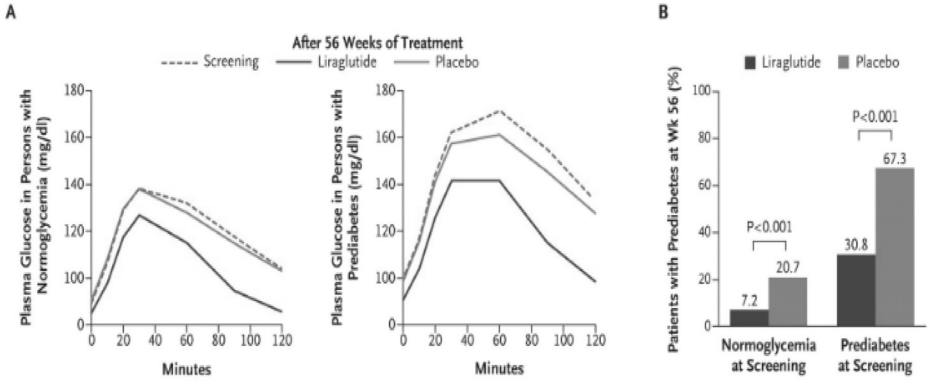
Effect of Liraglutide on Body weight



Astrup et al. Lancet 2009; 374 (901): 1606-16

Effect of Liraglutide on Obese Patients with Prediabetes

SCALE Obesity and Prediabetes (N=3.731)



Pi-Sunyer X , et al. N Engl J Med 2015;373: 11-22

Effect of Liraglutide on Cardiometabolic Risk Markers

SCALE study

Risk Factors	Liraglutide 3mg		P value
Systolic BP, mmHg	↓	-2.8	<0.0001
Diastolic BP, mmHg	↓	-0.6	NS
Triglycerides, %	↓	-6.0	0.0003
Total cholesterol, %	↓	-2.0	0.03
LDL-C, %	↓	-0.9	NS
HDL-C, %	↑	0.9	NS
VLDL-C, %	↓	-6.0	0.0002
FFAs, %	↓	-5.0	0.03
Waist circumference, cm	↓	-3.5	<0.0001

Fujioka et al. ENDO 2016, 1-4 April 2016, Abstract 24365

Adverse reactions of Liraglutide

	Placebo (n=1,941) %	Saxenda (n=3,384) %
Nausea	13.8	39.3
Diarrhea	9.9	20.9
Constipation	8.5	19.4
Vomiting	3.9	15.7
Dyspepsia	2.7	9.6
Abdominal Pain	3.1	5.4
Upper Abdominal Pain	2.7	5.1
Gastroesophageal Reflux Disease	1.7	4.7
Abdominal Distension	3.0	4.5
Eructation	0.2	4.5
Flatulence	2.5	4.0
Dry Mouth	1.0	2.3

Adverse reactions of Liraglutide - Nausea

- **Nausea was the most frequently reported GI disorder;**
  39% with Saxenda® vs 14% with placebo
- The percentage of patients reporting nausea declined as treatment continued.
- The most common adverse reaction leading to discontinuation was nausea (2.9% vs 0.2% for Saxenda and placebo, respectively)

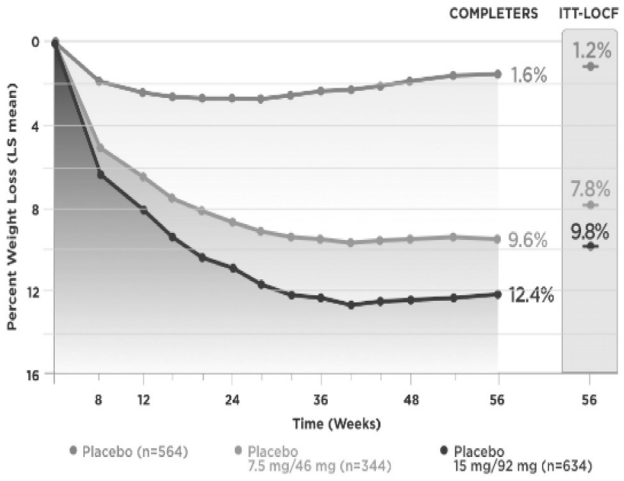
Phentermine/Topiramate (Qsymia®)

국내 시판허가(2019.7.) 출시 예정

•Central noradrenergic effects
- ✓ Phentermine: immediate-realease sympathomimetic-affects appetite
- ✓ Topiramate ER: delayed-release gabanergic-affect satiety

• Dosing
Starting dose: 3.75/23mg
Usual dose: 7.5/46mg
Maximum dose: 15/92mg

Effect of Phentermine/Topiramate on Body weight

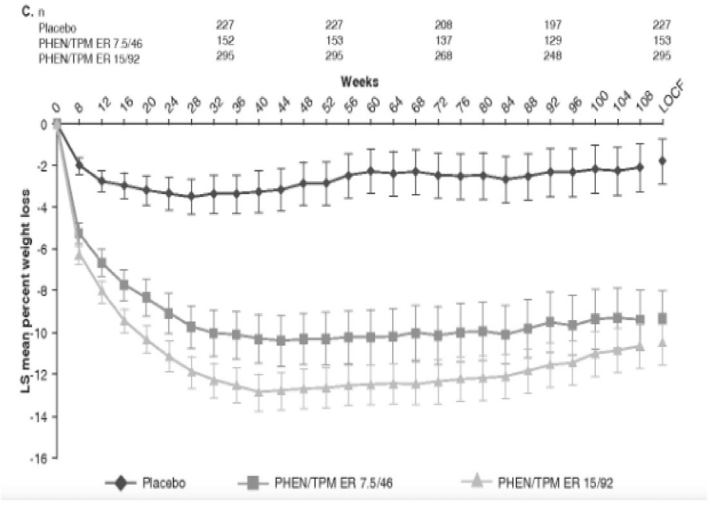


recommended dose

top dose

Gadde KM et al. Lancet 2011;377: 1341-1352

Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years



CONQUER Trial

SEQUEL Extension

Garvey WT et al. Am J Clin Nutr. 2012; 95(2): 297-308

Effect of Phentermine/Topiramate ER on Cardiometabolic Risk Markers

CONQUER study

Risk Factors	Phentermine/Topiramate 7.5/46mg		P value	Phentermine/Topiramate 7.5/46mg		P value
Systolic BP, mmHg	↓	-4.7	0.0008	↓	-5.6	<0.0001
Diastolic BP, mmHg	↓	-3.4	NS	↓	-3.8	0.0031
Triglycerides, %	↓	-8.6	<0.0001	↓	-10.6	<0.0001
Total cholesterol, %	↓	-4.9	0.0345	↓	-6.3	<0.0001
LDL-C, %	↓	-3.7	NS	↓	-6.9	0.0069
HDL-C, %	↑	5.2	<0.0001	↑	6.8	<0.0001
hsCRP, mg/L	↓	-2.49	<0.0001	↓	-2.49	<0.0001
Adiponectin, μg/mL	↑	1.40	<0.0001	↑	2.08	<0.0001

Gadde KM, et al. Lancet. 2011; 377: 1341-1352

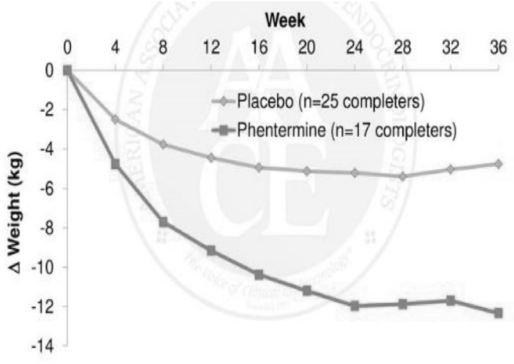
Adverse reactions of Phentermine/Topiramate ER

	Placebo (n=1,561) %	Phentermine/Topiramate ER %		
		3.75/23mg (N=240)	7.5/46mg (N=498)	15/92mg (1,580)
Paresthesia	1.9	4.2	13.7	19.9
Dry mouth	2.8	6.7	13.5	19.1
Constipation	6.1	7.9	15.1	16.1
Headache	9.3	10.4	7.0	10.6
Dysgenuria	1.1	1.3	7.4	9.4
Insomnia	4.7	5.0	5.8	9.4
Dizziness	3.4	2.9	7.2	8.6
Nausea	4.4	5.8	3.6	7.2
Fatigue	4.3	5.0	4.4	5.9

Phentermine

- Sympathomimetic amine anoretic
- Dosing
  : 15, 30, or 37.5 mg once daily before breakfast or 1-2hours after breakfast
- Trearment duration ≤ 12 weeks

Effect of Phentermine on Body weight



Munro JF, et al. Br Med J. 1968; 1: 352-354

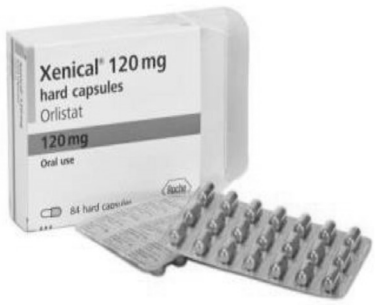
Adverse reactions of Phentermine

Cardiovascular	Primary pulmonary hypertension and/or regurgitant valvular disease, palpitation, tachycardia, BP elevations, ischemic events
Central nervous system	Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis
Gastrointestinal	Dryness of the mouth, unpleasant taste, diarrhea, constipation
Allergic	Urticaria
Endocrine	Impotence, changes in libido

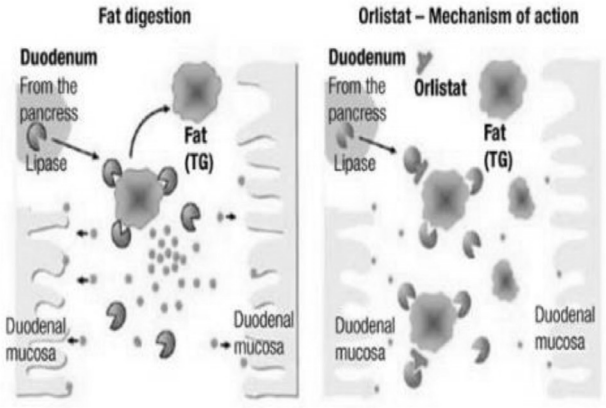
Orlistat (Xenical®)

- Reversible gastrointestinal lipase inhibitor

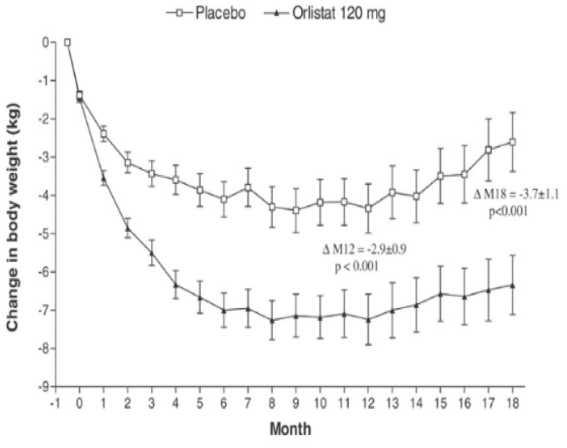
- Dosing
  120mg thrice daily with each meal containing fat
  Taken during or up to 1hour after eating



Orlistat Mechanism on Action



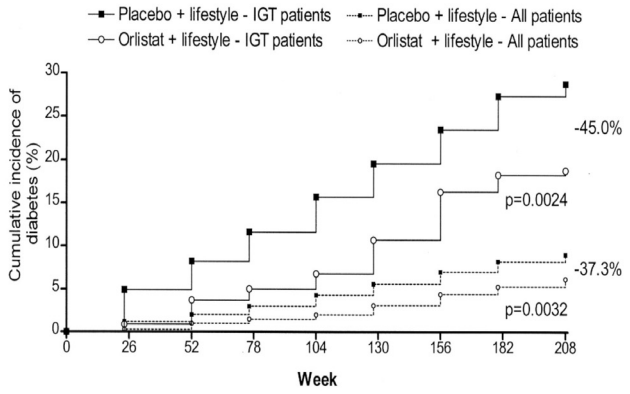
Effect of Orlistat on Body weight



M Krempf, et al. International Journal of Obesity 2003: 27, 591-597

Effect of Orlistat incidence of Diabetes in Obese Patients with Normal and Impaired Glucose Tolerance

XENDOS Study

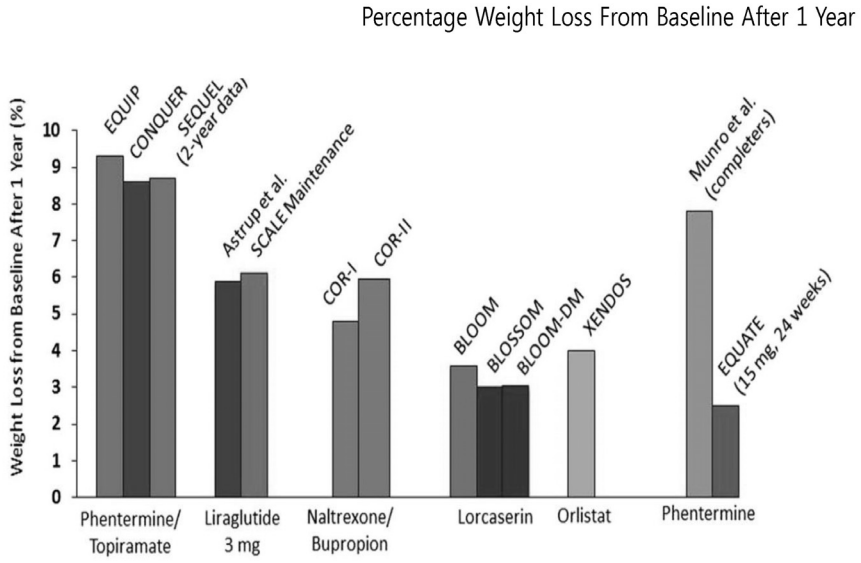


Torgerson JR, et al. Diabetes Care. 2004;27: 155-161

Adverse reactions of Orlistat

	Year 1		Year 2	
	Placebo (n=1,466)	Orlistat TID (n=1,913)	Placebo (n=524)	Orlistat TID (n=613)
Oily spotting	1.3	26.6	0.2	4.4
Flatus with discharge	1.4	23.9	0.2	2.1
Fecal urgency	6.7	22.1	1.7	2.8
Fatty/oily stool	6.7	20.1	1.7	2.8
Oily evacuation	0.8	11.9	0.2	2.3
Increased defecation	4.1	10.8	0.8	2.6
Fecal incontinence	0.9	7.7	0.2	1.8

Comparative Efficacy of Weight-Loss Medications



Comparative Efficacy of Weight-Loss Medications

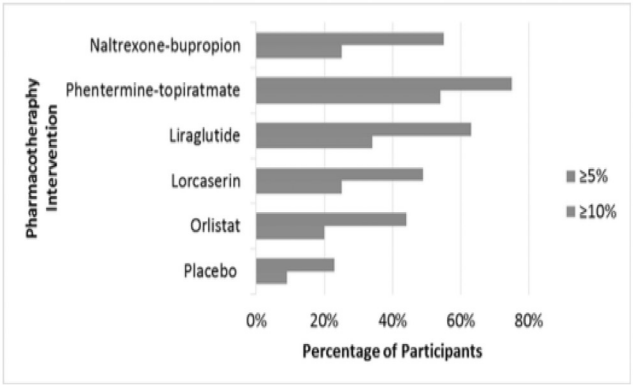
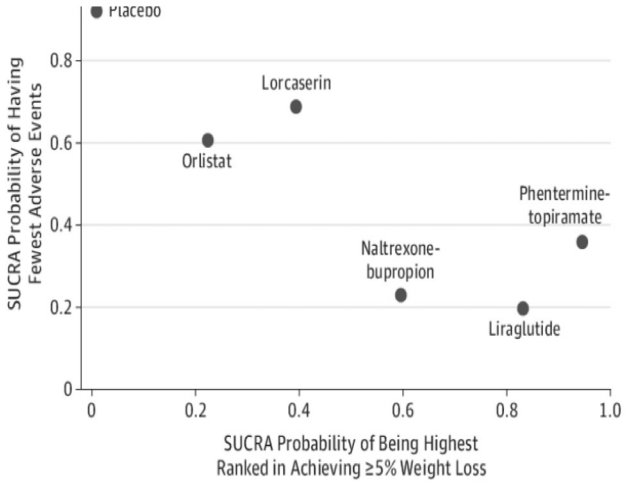


Figure 1. Weight loss at 1 year with pharmacotherapy combined with low-to-moderate intensity lifestyle counseling [41]. The median percentages of participants who had a weight loss of at least 5% or 10%, with each of five medications approved for long-term weight management and placebo, are shown.

Khera R, et al. JAMA 2016; 315: 2424-2434

Comparison of weight loss and adverse events



JAMA 2016; 315(22): 2424-34

Summary

- **Newer weight loss agents are typically better tolerated, have better safety profiles, and are approved for chronic weight management including weight maintenance**
- **Pharmacotherapy for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone**