Korean Society for Health Promotion and Disease Prevention

2020년 대한임상건강증진학회 동계학술대회

2020. 12. 6 (일)

비만약물치료

김 민 정 (미하나의원)

목 차

- 비만개론 : 비만정의,체중유지의 중요인자및 목표설정
- 비만약물 종류와 기전
- 비만약물 각론 : 큐시미아, 삭센다, 컨트라브
- 비만클리닉의 실제와 임상사례

비만

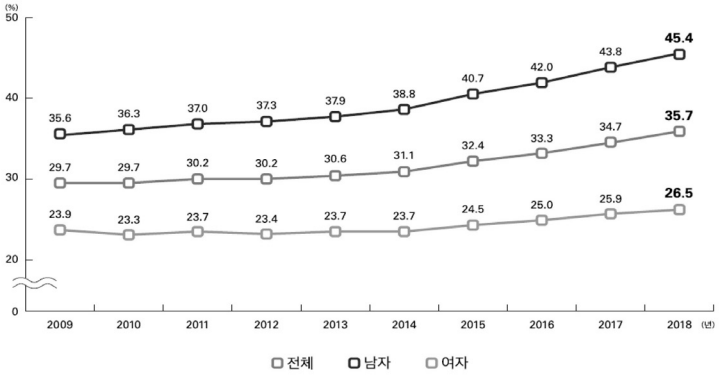
- 비만은 '지방이 비정상적으로 과도하게 축적되는 것.
- 체내에 과하게 축적된 지방조직은 다양한 질병 즉 당뇨나 고혈압, 고지혈증, 심혈관계질환 , 각종 암 을 일으킬 수 있는 만성질환.
- 1996년 세계보건기구(WHO) 비만은 '*치료해야하는 질병*'으로 규정.
- 최근에는 *21세기 신종 전염병* 이라고 함.
- 국내비만 유병률 1998년 26%에서 2013년 31.3%로 증가, 2015년 33.2% (2005년 비교 여성은 1.3%감소 남성 5% 증가) , 2016년 28.6% (남성 35.7% 여성 19.5%), 2018년 35.7%(남성 45.4% 여성 26.5%)

국내 비만 현황

최근 10년간 비만 유병률

최근 10년간 비만 유병률은 증가하였으며, 남자에서 크게 증가하였다.
2018년 비만 유병률은 35.7%이었으며, 남자에서 45.4%, 여자에서 26.5%였다.

45.4%
남자



비만의 치료

Obesity Algorithm®. ©2016-2017 Obesity Medicine Association

치료목표설정

지침

- **비만치료전에 환자가 체중을 감량할 준비가되었는지를 평가한후 치료목표는 개개인의 건강 상태와 조건에 맞게 현실적으로 정한다. (High A)**
- **비만치료의 목표는 비만 동반질환의 개선과 예방에 있다. (High A)**
- **치료전 체중의 3~5%를 감량하더라도 비만 동반질환을 의미있게 개선시킬 수 있다(High A)**
- **체중 감량의 일차 목표는 치료전 체중의 5~10%를 6개월내에 감량하는 것이다. (High A)**

대한비만학회 '비만치료지침 2014' A : 강하게 추천(환자에게 도움이 된다는 근거 충분) B중간추천C약하게추천D :추천안함
High : 대표적 무작위대조연구 Moderate : 약간제한적 무작위대조연구 Low: 제한많은 무작위대조연구

체중감량의 이득

Table 3. 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/m^2) increased risk of T2DM 4-fold.

Apovian CM. et al. J Clin Endocrinol Metab., 2015;100(2):342–362

비만약물치료

약물치료

- 비만의 기본적인 치료방법은 식사, 운동 및 행동 수정 용법이며 약물치료는 이들의 보조 적인 치료방법으로 사용할것을 권고한다 (High A)
- 비만치료제의 사용은 장기간(1년이상)사용이 가능한 약제와

  단기간 (12주이내) 사용이 가능한 약제로 나누어 사용하는 것을 고려한다. (High B)
- 비만치료제 사용시 생활습관교정을 병행할것을 권고한다 (High A)
- 약물치료 시작후 3개월내에 5~10%의 체중 감량이 없거나 동반질환의 개선 효과가 없으면 약제 변경이나 중단을 고려한다 (Low B)

대한비만학회 '비만치료지침 2014'

약물치료 적응증

- 체질량지수 25kg/m or 23kg/m + 심혈관계합병증 및 수면무호흡증이 있는경우 식사, 운동, 행동 요법에 병용치료로 이루어질수 있음

대한비만학회 '비만치료지침 2014'

약물치료

- 비만의 기본적인 치료방법은 식사, 운동 및 행동 수정 용법이며 약물치료는 이들의 보조 적인 치료방법으로 사용할것을 권고한다 (High A)
- 비만치료제의 사용은 장기간(1년이상)사용이 가능한 약제와 단기간 (12주이내) 사용이 가능한 약제로 나누어 사용하는 것을 고려한다. (High B)
- 비만치료제 사용시 생활습관교정을 병행할것을 권고한다 (High A)
- 약물치료 시작후 3개월내에 5~10%의 체중 감량이 없거나 동반질환의 개선 효과가 없으면 약제 변경이나 중단을 고려한다 (Low B)

대한비만학회 '비만치료지침 2018'

비만약물치료 역사

- 1880's ; thyroid extract (hyperthyroidism) *
- 1934 ; dinitrophenol (cataract, neuropathy) *
- 1937 ; amphetamines(addiction, CNS/cardiac toxic effect) *
- 1959 ; phendimetrazine
- 1959 ; phentermine
- 1959 ; diethylpropion
- 1967 ; rainbow pills- digitalis/diuretics (sudden death)
- 1972 ; fenfluramine (1997 fen-phen pulmonary hypertension) *
- 1973 ; mazindol
- 1997 ; sibutramine (2010 CV event) *
- 1999/2007 ; orlistat 120mg (Xenical), orlistat 60mg(Alli)
- 2006 ; rimonabant (2009 depression, suicide) *
- 2012; lorcaserin(2019 cancer) * , qsyimia
- 2014; contrave, liraglutide

1. Dietrich MO, et al. Nat Rev Drug Discov. 2012;11:675-691. 2. Contrave [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2014. 3. Saxenda [prescribing information]. Plainsboro, NJ: Novo Nordisk; 2014. 4. Yanovski SZ, et al. JAMA. 2014;311:74-86. 5. Apovian CM, et al. J Clin Endocrinol Metab. 2015;100:342-362.

비만 약물의 종류

1. 식욕 억제제 ; 식욕억제 효과로 섭취 칼로리 감소,

   norepinephrine, serotonin, dopamine

2. 흡수억제제 ; 지방흡수 억제제

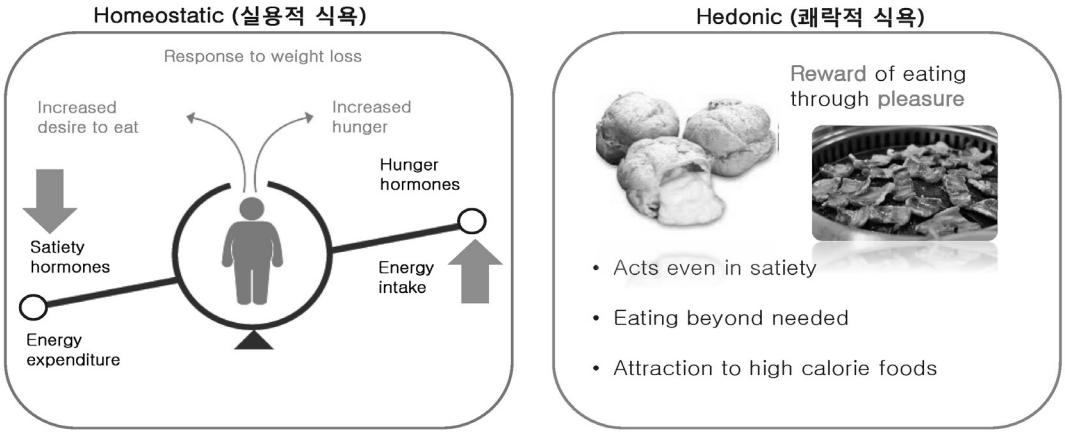
3. 열생산 촉진제 ; 기초대사량 증가

4. 기타 ; 포만감 증대제

   GABA receptor

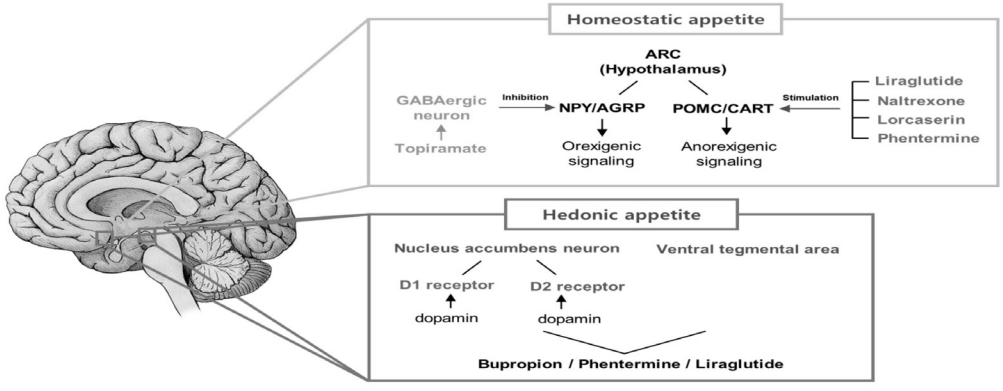
Ther Adv Drug Saf (2013) 4(4) 171–181

Homeostatic / Hedonic appetite



Hall *et al. Am J Public Health* 2014;104:1169-75

작용기전



Korean J Health Promot Vol. 19, No. 4, 2019

비만약물 – FDA approved

- ***Short term***
- Phendimetrazine – DEA 3 (Drug Enforecement Agency:DEA)
- Phentermine – DEA 4
- Mazindol - DEA 4
- Diethylpropion - DEA 4

- ***long term***
- Orlistat
- Qsymia ; phentermine / topiramate
- Contrave; bupropion 90mg / naltrexone 8mg
- Liraglutide ingection : GLP-1 agonost

비만약물 – off label

- Fluoxetine - antidepressant
- Bupropion – antidepressant, smoking cessation
- Topiramate – seizure disorder, migraine
- Naltrexone – opioid antagonist
- Ephedrine/ Caffeine

비만약물종류

1) Noradrenergic drug

• Norepinephrine 분비자극(Releaser) ; FDA 단기간 사용승인

- Phentermine(디에타민, 푸리민, 아디펙스..)
- Phendimetrazine (푸링, 펜디, 펜디씬..)
- Diethylpropion(디피온, 테뉴에이트..)

• Norepinephrine 재흡수 억제(reuptake inhibitor)

- Mazindol(사노렉스, 마자놀..)

2) serotonergic drug

Fenfluramine (5-HT stmulator: 1997년 FDA승인취소)

Sibutramine(SNRI) : 1997년 사용승인, 2010년 승인취소

Lorcaserin (벨빅): selective 5-HT 2c receptor agonist:2012년승인,2020년 퇴출

Fluoxetine (푸로작..):5-HT reuptake inhibitor: 우울증,신경성식욕과잉증에 승인

비만약물종류

3) Dopaminergic drug

• D2 agonist, reuptake 차단: bupropion(웰정, 콘트라브복합제)

4) GLP-1 agonist : Liraglutide

5) GABA, Glutamate : Topiramate

6) Thermogenic drug

• Ephedrine, Caffeine

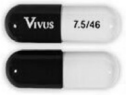
7) GI tract

• Orlistat(제니칼, 올리엣, 제로엑스..)

• Bulk-forming agent(alginic acid)

8) Etc

• Naltrexon(날트라); opioid antagonist



유지

큐시미아 Phentermine/Topiramate ER

Phentermine/Topiramate extended release

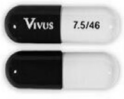
Phentermine (Maximum approved dose, 30 mg)

30

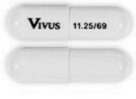
Topiramate (Maximum approved dose, 250 mg)

250

시작



유지

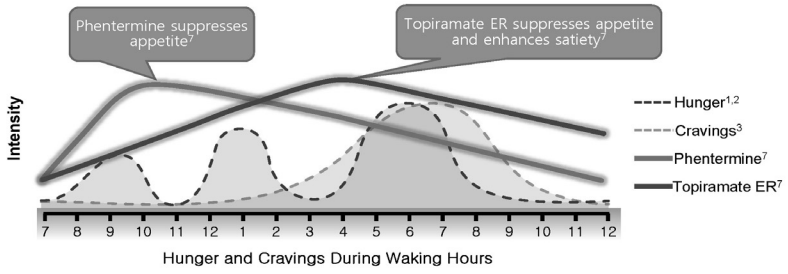


올림

TOP

- **Phen/Top ER Low (3.75/23)** **Starting dose**
- **Phen/Top ER Mid (7.5/46)** **Maintenance dose**
- **Phen/Top ER Top (15/92)** **For patients with <3% weight-loss after 12 weeks on Mid**

작용기전



큐시미아 : 펜터민의 즉각적인 식욕억제작용 + 토피라메이트의 식탐 및 폭식을 억제하는 작용이 결합 ➔ 하루 종일 식욕을 억제하고 포만감을 증가 [7]

[a]Hypothetical representation of hunger and cravings is not representative of all patients.
1. Hill AJ et al. *Appetite*. 1991;17(3):187-197. 2. Stubbs RJ et al. *Physiol Behav*. 2001;72(4):615-619. 3. Pelchat ML. *Appetite*. 1997;28(2):103-113. 4. Isaksson H et al. *Food Nutr Res*. 2008;52. 5. Hill AJ. *Proc Nutr Soc*. 2007;66(2):277-285. 6. Hill AJ, Heaton-Brown L. *J Psychosom Res*. 1994;38(8):801-814. 7. Phen/Top ER [prescribing information]. Mountain View, CA: VIVUS, Inc; 2014.

강력한 체중감소 효과

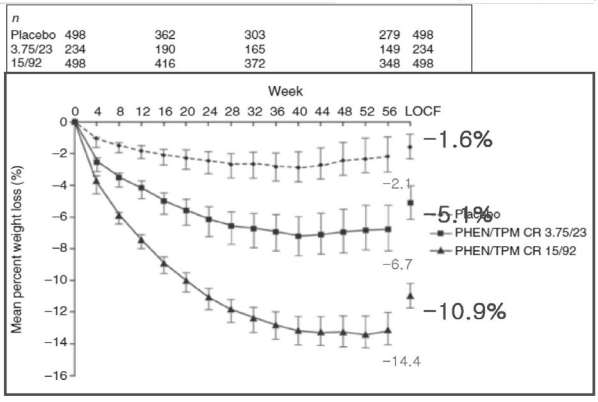
Treatment	Trial	Dose	N	Active - PBO
Saxenda	1839	Lira 3.0 mg Placebo	2487 1244	-4.5 -
	1922	Lira 3.0 mg Placebo	423 212	-3.7
	1923	Lira 3.0 mg Placebo	212 210	-5.2 -
Belviq	Studies 1 and 2 Combined	Belviq 10 mg BID Placebo	3098 3038	-3.3 -
	Study 3	Belviq 10 mg BID Placebo	251 248	-3.1 -
Contrave	COR-I	Contrave 32mg/360 mg Placebo	538 536	-4.1 -
	COR-BMOD	Contrave 32mg/360 mg Placebo	565 196	-3.2 -
	COR-Diabetes	Contrave 32mg/360 mg Placebo	321 166	-2.0-
Qsymia	EQUIP	Qsymia Low Qsymia Top Placebo	234 498 498	[illegible] -9.4
	CONQUER	Qsymia Mid Qsymia Top Placebo	488 981 979	-6.6 -8.6 -

EQUIP

1267명, BMI 35이상

Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP)

David B. Allison[1,2], Kishore M. Gadde[3], William Timothy Garvey[3,4], Craig A. Peterson[3], Michael L. Schwiers[5], Thomas Najarian[5], Peter Y. Tam[5], Barbara Troupin[5] and Wesley W. Day[5]



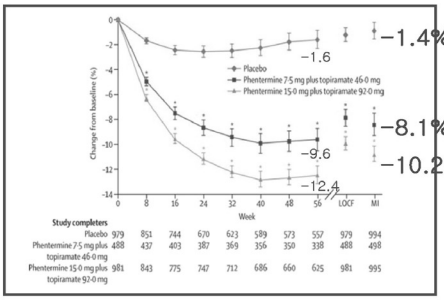
Obesity (2011) 20, 330–342. doi:10.1038/oby.2011.330

CONQUER

Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial

Kishore M Gadde, David B Allison, Donna H Ryan, Craig A Peterson, Barbara Troupin, Michael L Schwiers, Wesley W Day

2,487명, 2개이상(고혈압, 고지혈증, 당뇨병, 복부비만)



−1.4%
−8.1%
−10.2%

Figure 2. Effects of phentermine plus topiramate on bodyweight. LOCF, last observation carried forward; MI, myocardial; infarction. [Reprinted with permission from Gadde *et al.* [2011]. Copyright © 2011 Elsevier Science Ltd.] (BMI 27–45 with two or more comorbidities)

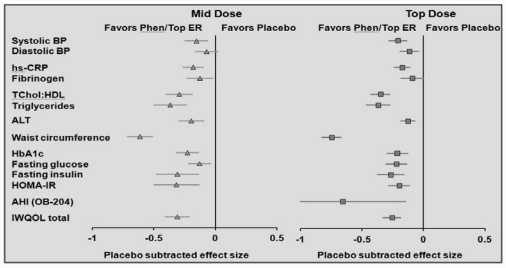
www.thelancet.com Vol 377 April 16, 2011

SEQUEL

Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study[1–3]

676명

Figure 3



Mean (95% confidence interval [CI]) percentage weight loss from baseline to week 108 from SEQUEL trial. LOCF: last observation carried forward, LS: least-squares, PHEN/TPM CR: controlled-release phentermine/topiramate. [Reprinted from "Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study", by Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, et al., 2012, Am J Clin Nutr, 95, pp.297-308. Copyright 2012 by the American Society for Nutrition. Reprinted with permission].

심혈관질환 위험인자 개선 및 안전성 (BP, HbA1c, chol 지표 호전, DM 발병 줄임, 부작용이 56-108주에는 감소)

Am J Clin Nutr 2012;95:297–308.

심혈관계–EQUATE

Evaluation of Phentermine and Topiramate versus Phentermine/Topiramate Extended-Release in Obese Adults

Louis J. Aronne[1], Thomas A. Wadden[2], Craig Peterson[3], David Winslow[4], Sarah Odeh[5] and Kishore M. Gadde[6]

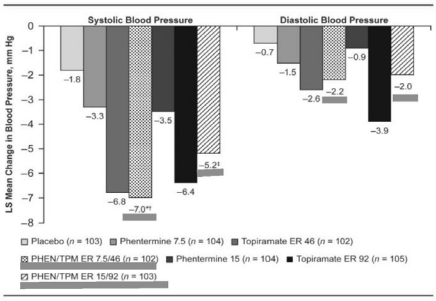


FIGURE 3 LS mean change in systolic and diastolic blood pressure from baseline to week 28 in the ITT-LOCF population. *P = 0.0004 vs. placebo; †P = 0.0108 vs. phentermine 7.5; ‡P = 0.0224 vs. placebo. ITT, intention-to-treat; LOCF, last observation carried forward; LS, least squares; PHEN/TPM ER 15/92, phentermine 15 mg and topiramate extended-release 92 mg; PHEN 15, phentermine 15 mg; TPM ER 92, topiramate extended-release 92 mg; PHEN/TPM ER 7.5/46, phentermine 7.5 mg and topiramate extended-release 46 mg; PHEN 7.5, phentermine 7.5 mg; TPM ER 46, topiramate extended-release 46 mg.

TABLE 5 Changes in heart rate from baseline to week 28 (safety set)

	Placebo	Phentermine 7.5	Topiramate ER 46	PHEN/TPM ER 7.5/46	Phentermine 15	Topiramate ER 92	PHEN/TPM ER 15/92
Heart rate (bpm)							
n	74	79	78	78	80	77	75
Baseline mean (SD)	72.4 (9.74)	72.9 (9.57)	72.2 (9.54)	72.8 (9.96)	72.5 (10.64)	73.4 (9.49)	72.7 (9.57)
Mean change (SD)	−1.9 (9.42)	0.9 (9.90)	−3.8 (10.00)	−1.6 (10.46)	1.1 (10.57)	−4.5 (9.13)	−1.6 (11.66)

n is the number of subjects with a measurement at both baseline and week 28.
bpm, beats per minute; PHEN/TPM ER 7.5/46, phentermine 7.5 mg and topiramate extended-release 46 mg; PHEN/TPM ER 15/92, phentermine 15 mg and topiramate extended-release 92 mg; SD, standard deviation.

금기및 안정성

CONTRAINDICATIONS

- Pregnancy(fetal toxicity - oral clefts)
- Glaucoma
- Hyperthyroidism
- MAOIs 14일 이내 사용
- 과민반응, 18세 미만, 심혈관계 질환 환자, uncontrolled HTN, 폐동맥고혈압, 약물남용

SAFETY

- Psychiatric AEs, cognitive AEs
- No suicidality signal in Phen/Top ER vs placebo
- Increased heart-rate outlier patients showed concomitant decreases in blood pressure and rate pressure product
- There was no increase in MACE composite hazard ratios compared to placebo

Liraglutide(Saxenda)

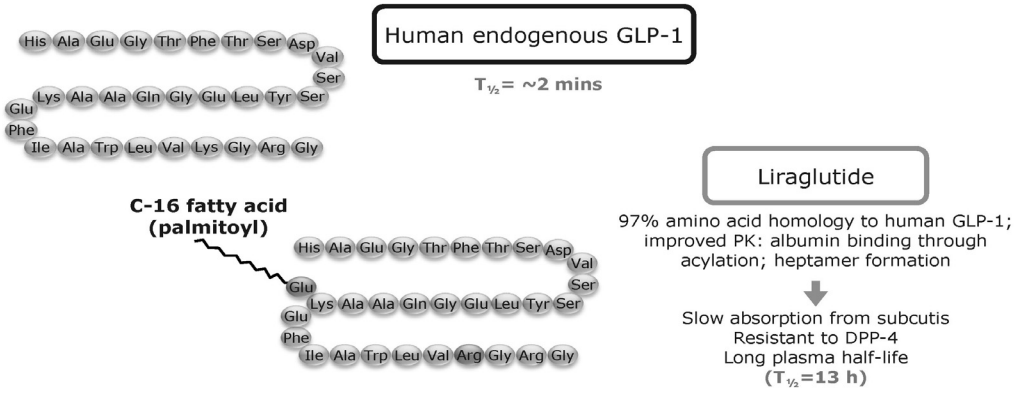
특징및 기전

- FDA Approved in 2014, Korea in 2017 7/21
- Indication :BMI 30 kg/m2 greater or 27 kg/m2 greater and comorbidity
- Dose : 3mg SQ daily
- GLP-1 agonist : appetite/gasric emptying time 감소, insulin 분비증가
- SCALE Clinical trial : 56wks 5% wt loss-placebo /saxenda 27% / 63%,

: decrease in triglycerides, insulin resistance, BP / increase in HDL-C

- 장점: 다른비만약물과 상호작용이 적음, 당뇨 혈압 지질 개선효과, 비향정
- 단점 : 주사, 위장관부작용, 가격부담
- 부작용 : 오심/ 구토, 설사/변비, 두통, 어지러움, 급성췌장염, 담석증등
- 금기 : 갑상선수질암 환자나 가족력, 임부, 수유부

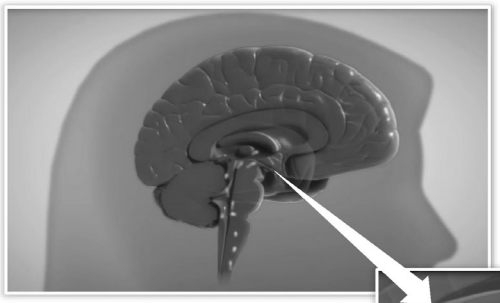
Liraglutide is a once-daily, human GLP-1 analogue



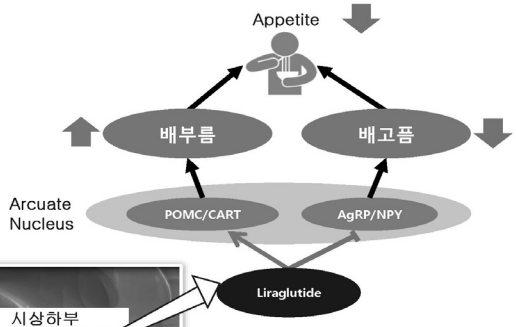
DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PK, pharmacokinetics; $T_{½}$, plasma half-life

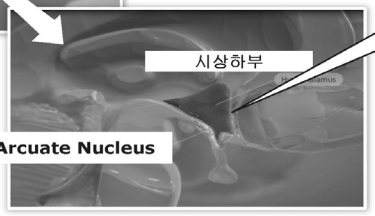
Knudsen *et al. J Med Chem* 2000;43:1664–9; Degn *et al. Diabetes* 2004;53:1187–94

특징및 기전



Homeostatic and hedonic regulation of appetite





Secher *et al. J Clin Invest* 2014;124:4473–88; van Can *et al. Int J Obes (Lond)* 2014;38:784–93

SCALE Phase 3a clinical trial

SCALE Obesity and Prediabetes (1839)[1]

Weight management & delayed onset of diabetes
- Liraglutide 3.0 mg n=2487
- Placebo n=1244

SCALE Maintenance (1923)[3]

Prevention of weight regain
- Liraglutide 3.0 mg n=212
- Placebo n=210

SCALE Diabetes (1922)[2]

Weight management in type 2 diabetes
- Liraglutide 3.0 mg n=423
- Liraglutide 1.8 mg n=211
- Placebo n=212

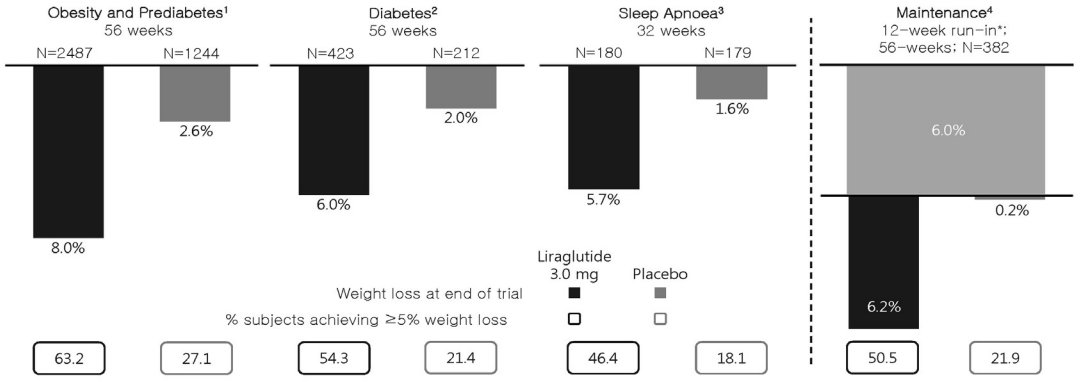
SCALE Sleep Apnoea (3970)[4]

Effect of liraglutide in subjects with obesity and moderate to severe OSA
- Liraglutide 3.0 mg n=180
- Placebo n=179

*SCALE, Sleep apnoea 3970 trial BMI ≥30 kg/m² plus co-morbidities;
BMI, body mass index; OSA, obstructive sleep apnoea; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence in individuals with and without diabetes

1. Pi-Sunyer *et al. N Engl J Med* 2015;373:11–22; 2. Davies *et al. JAMA* 2015;314:687–99; 3. Wadden *et al. Int J Obes (Lond)* 2013;37:1443–51; 4. Blackman *et al. Int J Obes (Lond).* 2016;40:1310-9

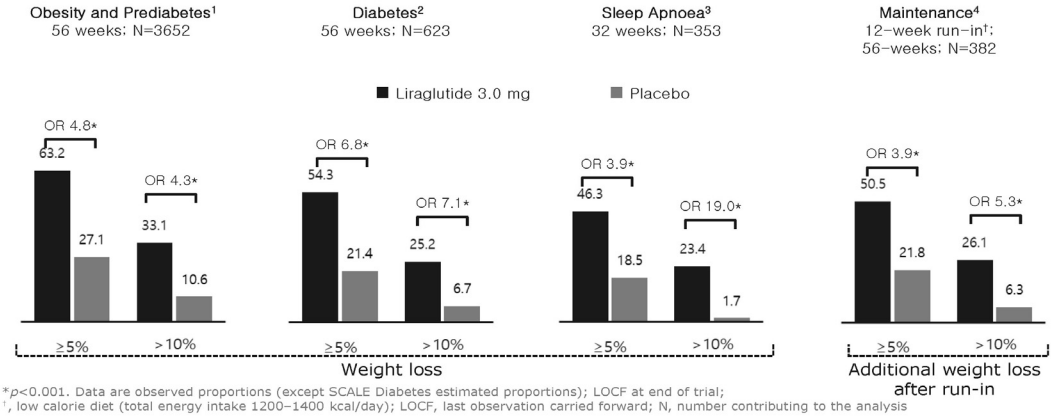
Weight loss across SCALE trials



Data are observed means/proportions (except SCALE Diabetes estimated LS means/proportions); LOCF at end of trial.
*, low calorie diet (total energy intake 1200–1400 kcal/day); LOCF, last observation carried forward; LS, least-squared; N, number contributing to the analysis

1. Pi-Sunyer *et al. N Engl J Med* 2015;373:11–22; 2. Davies *et al. JAMA* 2015;314:687–99; 3. Blackman *et al. Int J Obes (Lond).* 2016;40:1310-9;
4. Wadden *et al. Int J Obes (Lond)* 2013;37:1443–51

Categorical weight loss across SCALE trials

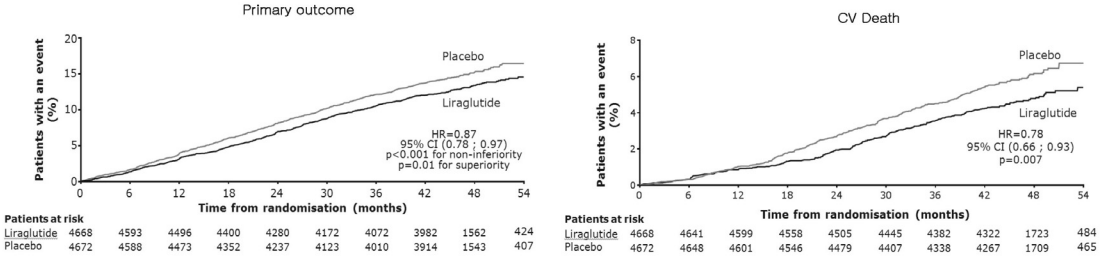


*p<0.001. Data are observed proportions (except SCALE Diabetes estimated proportions); LOCF at end of trial;
†, low calorie diet (total energy intake 1200–1400 kcal/day); LOCF, last observation carried forward; N, number contributing to the analysis

1. Pi-Sunyer *et al. N Engl J Med* 2015;373:11–22; 2. Davies *et al. JAMA* 2015;314:687–99;
3. Blackman *et al. Int J Obes (Lond).* 2016;40:1310-9;
4. Wadden *et al. Int J Obes (Lond)* 2013;37:1443–51

LEADER trial

Risk reduction in primary outcome & CV Death for liraglutide vs. placebo
▼13% in primary outcome & ▼ 22% in CV Death



in more than 9,000 patients for period upto 5 years
in T2D patients with liraglutide at dose upto 1.8 mg

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Adverse effects

Table 3. **Adverse Events and Serious Adverse Events.***

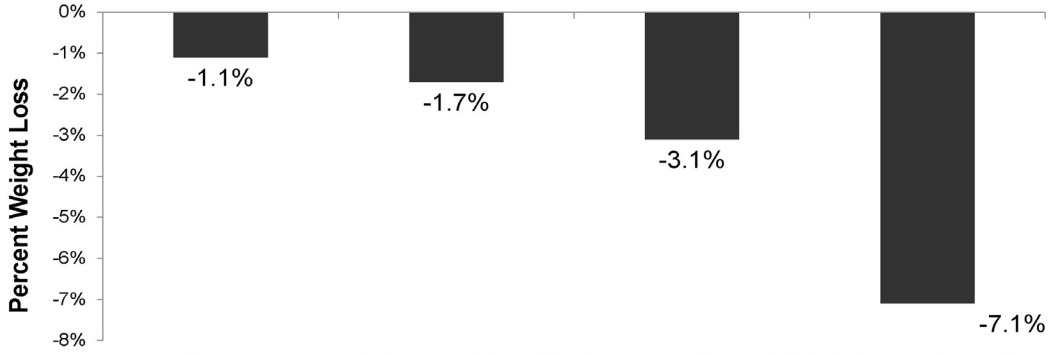
Event	Liraglutide (N = 2481)			Placebo (N = 1242)		
	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years
Adverse events in ≥5% of patients	1992 (80.3)	7191	321.8	786 (63.3)	2068	193.7
Nausea	997 (40.2)	1429	63.9	183 (14.7)	223	20.9
Diarrhea	518 (20.9)	754	33.7	115 (9.3)	142	13.3
Constipation	495 (20.0)	593	26.5	108 (8.7)	121	11.3
Vomiting	404 (16.3)	597	26.7	51 (4.1)	62	5.8
Dyspepsia	236 (9.5)	282	12.6	39 (3.1)	44	4.1
Upper abdominal pain	141 (5.7)	171	7.7	43 (3.5)	49	4.6
Abdominal pain	130 (5.2)	163	7.3	43 (3.5)	53	5.0
Nasopharyngitis	427 (17.2)	586	26.2	234 (18.8)	302	28.3
Upper respiratory tract infection	213 (8.6)	247	11.1	122 (9.8)	149	14.0
Sinusitis	128 (5.2)	141	6.3	73 (5.9)	95	8.9
Influenza	144 (5.8)	170	7.6	66 (5.3)	84	7.9
Headache	327 (13.2)	441	19.7	154 (12.4)	220	20.6
Dizziness	167 (6.7)	203	9.1	60 (4.8)	65	6.1
Decreased appetite	267 (10.8)	283	12.7	38 (3.1)	39	3.7
Back pain	171 (6.9)	210	9.4	105 (8.5)	121	11.3
Arthralgia	125 (5.0)	133	6.0	71 (5.7)	80	7.5
Fatigue	185 (7.5)	203	9.1	65 (5.2)	72	6.7
Injection-site hematoma	142 (5.7)	154	6.9	93 (7.5)	101	9.5
Serious adverse events in ≥0.2% of patients	154 (6.2)	194	8.7	62 (5.0)	75	7.0
Cholelithiasis	20 (0.8)	20	0.9	5 (0.4)	5	0.5
Cholecystitis acute	12 (0.5)	12	0.5	0	0	0.0
Osteoarthritis	6 (0.2)	7	0.3	0	0	0.0
Intervertebral disc protrusion	5 (0.2)	5	0.2	1 (0.1)	1	0.1
Pancreatitis acute†	4 (0.2)	4	0.2	0	0	0.0
Cholecystitis	4 (0.2)	4	0.2	0	0	0.0
Breast cancer	4 (0.2)	4	0.2	1 (0.1)	1	0.1
Back pain	2 (0.1)	2	<0.1	2 (0.2)	2	0.2
Uterine leiomyoma	1 (<0.1)	1	<0.1	2 (0.2)	2	0.2
Cellulitis	1 (<0.1)	1	<0.1	3 (0.2)	3	0.3
Gastroesophageal reflux disease	0	0	0.0	2 (0.2)	2	0.2
Bronchitis	0	0	0.0	2 (0.2)	2	0.2
Bladder prolapse	0	0	0.0	2 (0.2)	2	0.2
Chest pain	0	0	0.0	3 (0.2)	3	0.3

* Adverse events and serious adverse events that occurred up to and including week 58 among patients in the safety-analysis set are included and are presented by their preferred terms from the Medical Dictionary for Regulatory Activities. Events are included if they had an onset date on or after the first day the study drug was administered and no later than 14 days after the last day the study drug was administered.
† "Pancreatitis acute" was reported as serious by the investigator but was classified as mild according to revised Atlanta classification of acute pancreatitis.[7]

Contrave

Naltrexone & Bupropion: Synergistic Pharmacology for Weight Loss

Phase 2b Completers' Weight Loss at 24 Weeks



- Indicated for the treatment of alcohol and opioid dependence
- Indicated for the treatment of depression and smoking cessation

Data are for completer population. IR=immediate release; SR=sustained release.

1. Greenway FL, et al. *J Clin Endocrinol Metab.* 2009;94:4898-4906.

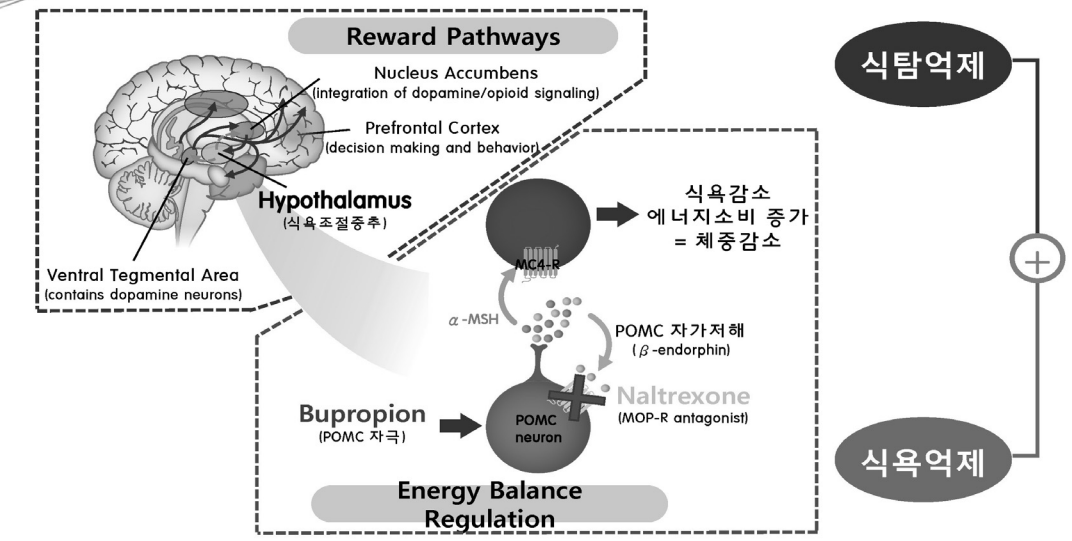
작용기전과 특징

- 4T(Naltrexone 8 mg/ Bupropion 90 mg 2 tablets BID) (high dose)
  (achieved after 4 weeks)
- • CONTROl + crAVE "음식에 대한 갈망(식탐)을 조절한다"
- Bupropion - dopamine & norepinephrine reuptake inhibitor
  → effects on POMC signaling,
  Naltrexone - opioid receptor antagonist
  → weight-loss effects

- 특징: Food addiction에 효과적, 비향정신성 약물, 음주나 흡연에도 도움
- 단점 : 고가 3400원/일(850원4T), 용량조절 필요, 식욕억제효과 상대적으로 적음

1. Naltrexone/Bupropion ER [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2014.

콘트라브 작용기전



Bupropion으로	재흡수가 억제된 도파민이 POMC 자극, 활성화	→	α-MSH가 MC4-수용체에 결합	→ 식욕억제
Naltrexone은	오피오이드 길항제	→	β-endorphin에 의한 POMC 자가저해 억제	→ POMC 활성 지속 → 식욕억제

POMC: Pro-opiomelanocortin, α-MSH: α-melanocyte stimulating hormone, MC4-R: Melanocortin 4 receptor, MOP-R: mu-opioid receptor

사용방법 주의점

- **Indication**

  - 체질량지수 **25 kg/m²** 이상인 경우, 혹은 **23 kg/m²** 이상이면서 **1개 이상의 비만 관련 합병증**(고혈압, 당뇨병 및 이상지질혈증이나 수면무호흡증)이 동반된 환자

- **용량, 용법**

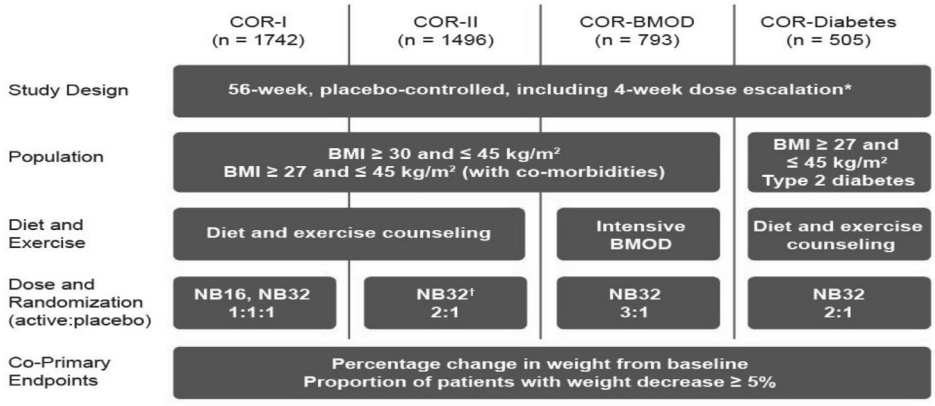
  - 1 Tablet : 8 mg naltrexone/ 90mg bupropion (2 tablets twice daily).

Naltrexone/Bupropion ER dosing should be escalated over a 4-week period		
	Morning	Evening
Week 1	●	
Week 2	●	●
Week 3	● ●	●
Week 4 and onwards	● ●	● ●

- **S/E:** nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth and diarrhea
- **Responsiveness;** weight loss > 5% during 12 weeks

Naltrexone/Bupropion ER [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2014.

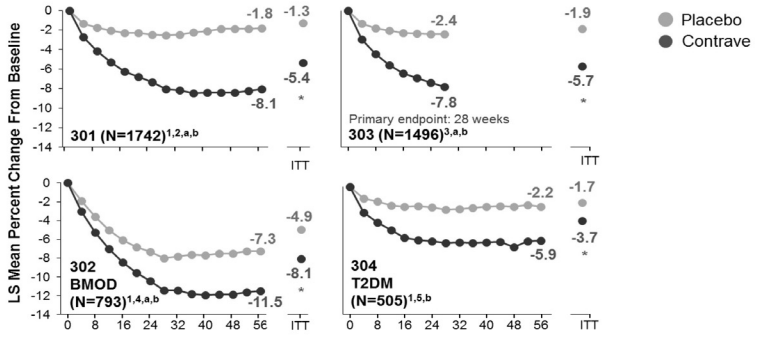
Clinical trials



* For COR-II, full dose was reached by the start of week 5
† With exploration of NB48 in NB32 non-responders

1. Greenway FL, et al. Lancet. 2010;376:595-605. 2. Apovian CM, et al. Obesity. 2013;21:935-943. 3. Wadden TA, et al. Obesity. 2011;19:110-120 4. Hollander P, et al. Diabetes Care. 2013;36:4022-4029.

Weight change : 1차 유용성 체중감량



*P<0.001 versus placebo.
[a]BMI 30–45 kg/m^2.
[b]BMI 27–45 kg/m^2 with comorbidities.
BMOD=behavior modification; ITT=intent-to-treat; LS=least squares; T2DM=type 2 diabetes mellitus.
Top right figure adapted from Apovian et al,[3] © 2013 The Obesity Society, with permission from John Wiley and Sons.
Bottom right figure republished with permission of the American Diabetes Association, from Hollander et al,[5] © 2013; permission conveyed through Copyright Clearance Center, Inc.
1. Contrave [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2014. **2.** Greenway FL, et al. *Lancet.* 2010;376:595-605. **3.** Apovian CM, et al. *Obesity.* 2013;21:935-943. **4.** Wadden TA, et al. *Obesity.* 2011;19:110-120. **5.** Hollander P, et al. *Diabetes Care.* 2013;36:4022-4029.

Side Effects

	Placebo (n=569)	Naltrexone 16 mg plus bupropion (n=569)	Naltrexone 32 mg plus bupropion (n=573)
Adverse events			
Participants reporting any adverse event	390 (68·5%)	455 (80·0%)†	476 (83·1%)†
Nausea	30 (5·3%)	155 (27·2%)†	171 (29·8%)†
Headache	53 (9·3%)	91 (16·0%)†	79 (13·8%)†
Constipation	32 (5·6%)	90 (15·8%)†	90 (15·7%)†
Upper respiratory tract infection	64 (11·2%)	49 (8·6%)	57 (9·9%)
Dizziness	15 (2·6%)	44 (7·7%)†	54 (9·4%)†
Insomnia	29 (5·1%)	36 (6·3%)	43 (7·5%)
Vomiting	14 (2·5%)	36 (6·3%)†	56 (9·8%)†
Sinusitis	34 (6·0%)	34 (6·0%)	30 (5·2%)
Dry mouth	11 (1·9%)	42 (7·4%)†	43 (7·5%)†
Nasopharyngitis	31 (5·4%)	32 (5·6%)	29 (5·1%)
Diarrhoea	28 (4·9%)	31 (5·4%)	26 (4·5%)
Hot flush	7 (1·2%)	13 (2·3%)	30 (5·2%)†
Participants reporting any psychiatric adverse event	62 (10·9%)	76 (13·4%)	85 (14·8%)
Insomnia	29 (5·1%)	36 (6·3%)	43 (7·5%)
Anxiety	12 (2·1%)	12 (2·1%)	9 (1·6%)
Depression	6 (1·1%)	9 (1·6%)	3 (0·5%)

Safety endpoints‡			
Systolic blood pressure (LOCF; mm Hg)			
Baseline	119·0 (9·8)	119·3 (9·9)	119·0 (9·8)
Change	−2·1 (0·4)	0·2 (0·4)†	−0·4 (0·4)†
Systolic blood pressure (observed; mm Hg)			
Baseline	119·7 (9·7)	119·5 (9·9)	118·9 (9·5)
Change	−2·8 (0·5)	−0·4 (0·5)†	−1·6 (0·5)
Diastolic blood pressure (LOCF; mm Hg)			
Baseline	77·3 (6·7)	76·6 (7·2)	77·1 (7·2)
Change	−1·0 (0·3)	−0·0 (0·3)†	−0·1 (0·3)†
Diastolic blood pressure (observed; mm Hg)			
Baseline	77·5 (6·7)	76·2 (7·4)	77·1 (7·2)
Change	−1·4 (0·4)	−0·5 (0·4)	−0·8 (0·4)
Pulse rate (LOCF; beats per min)			
Baseline	71·8 (8·0)	71·4 (8·7)	72·0 (8·7)
Change	−0·1 (0·3)	1·5 (0·3)†	1·0 (0·3)†
Pulse rate (observed; beats per min)			
Baseline	71·6 (7·9)	71·1 (8·6)	72·4 (8·6)
Change	−1·0 (0·4)	1·1 (0·4)†	0·4 (0·4)†

Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I) a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial Frank L Greenway etc., Lancet 2010; 376: 595–605

Contraindications

- Uncontrolled hypertension
- Seizure disorder or a history of seizures
- Use of other bupropion-containing products (including, but not limited to, Wellbutrin, Wellbutrin SR, Wellbutrin XL, and Aplenzin)
- Bulimia or anorexia nervosa, which increase the risk for seizures
- Chronic opioid or opiate agonist or partial agonists use, or acute opiate withdrawal
- Patients undergoing an abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs
- Concomitant administration of monoamine oxidase inhibitors (MAOI)
  - At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with naltrexone/bupropion
- Known allergy to bupropion, naltrexone or any other component of Contrave
  - Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion
- Pregnancy

1. Contrave [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2014.

결론

- 비만은 지방이 비정상적으로 과도하게 축적되는 것으로 당뇨나 고혈압, 고지혈증, 심혈관계질환 , 암등을 일으킬 수 있는 만성질환.
- 식욕관련 신경전달물질 norepinephrine, serotonin, dopamine이 있다.
- 약물치료는 비만의 식사, 운동, 행동수정치료와 더불어 중요한 수단이다.
- 큐시미아, 콘트라브, 삭섹다는 최근 FDA에 승인된 새로운 약물로 초기 감량 및 유지요법으로 기대할 만 하다.
- 초기체중감량과 함께 유지치료가 매우 중요하다.