Korean Society for Health Promotion and Disease Prevention

2021년 대한임상건강증진학회 춘계학술대회

2021. 5. 30 (일)

# 비만 치료의 최신 경향

김 민 정 (미하나의원)

# 목 차

- 비만개론
- 비만약물 종류와 기전
- 비만약물 각론 : 큐시미아, 컨트라브, 삭센다
- 비만클리닉의 실제와 임상사례

# 비만

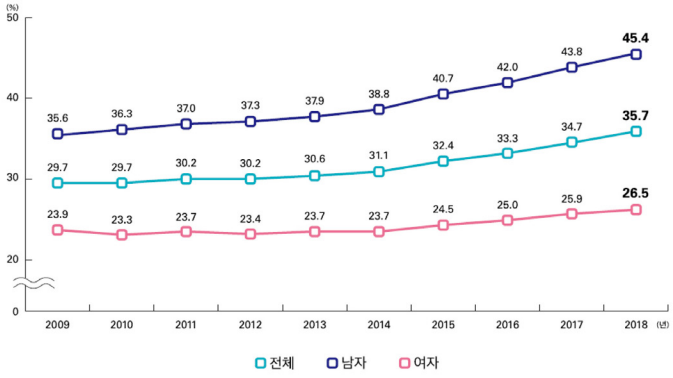
- 비만은 '지방이 비정상적으로 과도하게 축적되는 것.
- 체내에 과하게 축적된 지방조직은 다양한 질병 즉 당뇨나 고혈압, 고지혈증, 심혈관계질환 , 각종 암 을 일으킬 수 있는 만성질환.
- 1996년 세계보건기구(WHO) 비만은 '*치료해야하는 질병*'으로 규정.
- 최근에는 *21세기 신종 전염병* 이라고 함.
- 국내비만 유병률 1998년 26%에서 2013년 31.3%로 증가, 2015년 33.2% (2005년 비교 여성은 1.3%감소 남성 5% 증가) , 2016년 28.6% (남성 35.7% 여성 19.5%), 2018년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




# 비만과 관련 질환

- 대사적이상 :

  제2형 당뇨병, 고지혈증, 대사증후군,

  담낭질환, 관상동맥질환, 고혈압, 암 등


- 과도한 체중 : 골관절염, 요통, 수면무호흡증 등
- 정신적 문제 : 자신감 결여, 우울증, 대인관계 기피증, 사회부적응

# 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

# 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'*

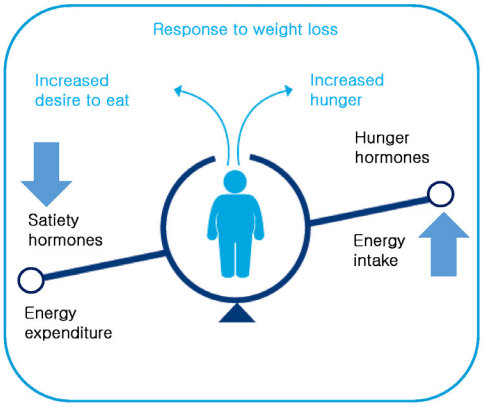
## 약물치료 적응증

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

*대한비만학회 '비만치료지침 2014'*

# Homeostatic / Hedonic appetite

Homeostatic (실용적 식욕)



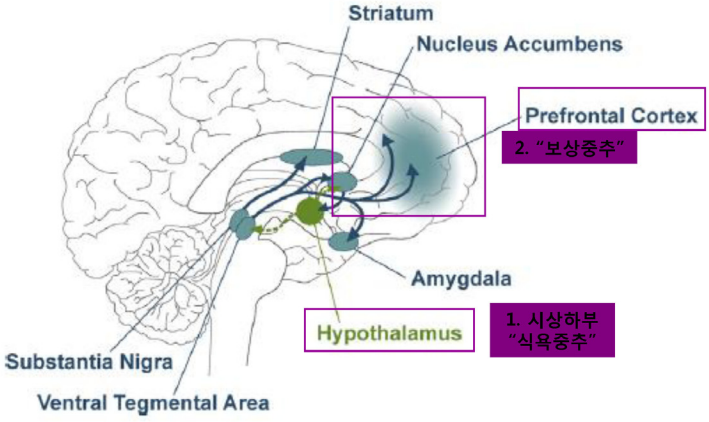

Hedonic (괘락적 식욕)


- Acts even in satiety
- Eating beyond needed
- Attraction to high calorie foods

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

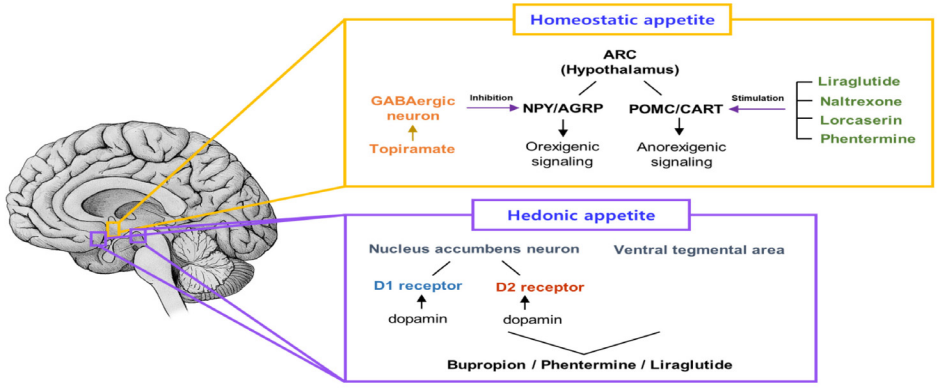
# 식욕조절중추

**에너지의 섭취/소비 균형(항상성)은 뇌에 의해 조절.**




Billes SK, et al. Pharmacological Research . 2014;84:1-11 .

# 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

## 큐시미아 Phentermine/Topiramate ER

## Phentermine/Topiramate extended release

Phentermine (Maximum approved dose, 30 mg)

30

Topiramate (Maximum approved dose, 250 mg)

250

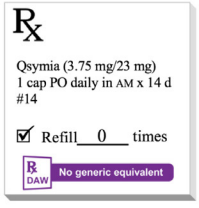

- **Phen/Top ER Low (3.75/23)** **Starting dose**
- **Phen/Top ER Mid (7.5/46)** **Maintenance dose**
- **Phen/Top ER Top (15/92)** **For patients with <3% weight-loss after 12 weeks on Mid**

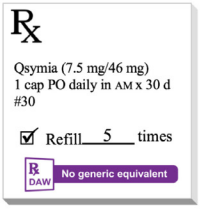
## 4 Dosing for Individualized Pt

### Initiating Therapy

**Write 2 Prescriptions :**

| | | |
|---|---|---|
| **Weeks 1-2** | **Starter Dose**<br>**Start patients on 2 weeks on Qsymia 3.75mg/23 mg.** Patients may or may not lose weight during this starter dose period. Encourage them to move on to the recommended therapeutic dose for weight loss. |  |
| **Weeks 3-12+** | **Recommended Dose**<br>**On week 3, start patient on the recommended dose of Qsymia 7.5 mg/46 mg.**<br>Patients may receive up to 5 refills of the recommended dose of Qsymia |  |




[a]Pills not shown as actual size.

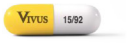
Qsymia [package insert]. Campbell, CA: VIVUS, Inc; 2017.

# Adjust Dosing

## Evaluating Patients After 12 Weeks

If a patient does not attain a ≥3% weight loss after 12 weeks of treatment at the recommended dose (7.5 mg/46 mg) of Qsymia, either discontinue Qsymia or escalate dose.

**To escalate Qsymia dose, write 2 prescriptions:**

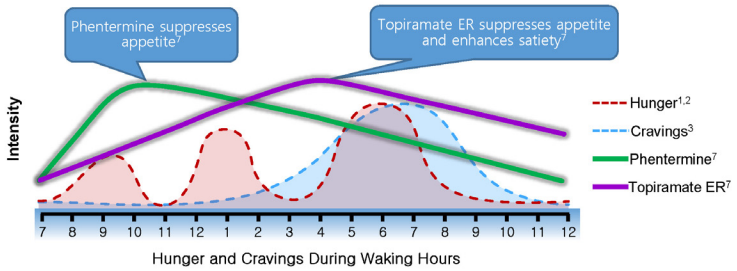
| | | |
|---|---|---|
| **Weeks 13-14** | **Titration Dose**<br>**Start patients on 2 weeks on Qsymia 11.25 mg/69 mg.** The patient should stay on this dose for 2 weeks. |  |
| **Weeks 15+** | **High Dose**<br>**Continue patient with monthly prescriptions on Qsymia 15 mg/92 mg.** Continue to monitor patient's progress at each visit and reevaluate weight loss after patient has been on the top dose for 12 weeks. |  |

**After 12 weeks on the top dose (15 mg/92 mg), if weight loss is <5% discontinue treatment with Qsymia. Refer to Full Prescribing Information for tapering Qsymia 15 mg/92 mg gradually and suggested follow-ups.**

[a]Pills not shown as actual size.

Qsymia [package insert]. Campbell, CA: VIVUS, Inc; 2017.

# 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.

# EQUIP

ARTICLES
INTERVENTION AND PREVENTION
nature publishing group
Open

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[2,4], Craig A. Peterson[2], Michael L. Schwiers[6], Thomas Najarian[5], Peter Y. Tam[5], Barbara Troupin[5] and Wesley W. Day[5]

- **56 주**
- BMI ≥ 35 kg/m2 환자
- Placebo (n = 514), **PHEN/TPM CR 3.75/23 mg** (n = 241)
  **PHEN/TPM CR 15/92 mg** (n = 512)
- **Primary endpoint :** 연구 종료 시 5%, 10%, 15% 체중 감소한 비율

Ref. Controlled-Release Phentermine/Topiramate in Severely Obese adults: a Randomized Controlled Trial (EQUIP), 2012

# 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*

- **3상 임상, 56주** (randomised, double-blind, placebo controlled study)
- BMI of 27–45 kg/m² and 2개이상 동반 질환
  (고혈압, 이상지질혈증, 당뇨, 복부비만)
- Once daily, Placebo vs. **phentermine 7·5/topiramate 46 mg vs. phentermine 15/topiramate 92 mg**
- 피실험자2,487명, 미국 내 93개 기관
- **Primary endpoint :** 체중변화율, 최소 5% 이상 체중 감소에 성공한 환자 비율

Ref. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER), 2011

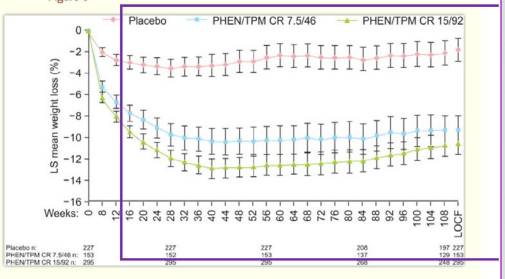
# SEQUEL

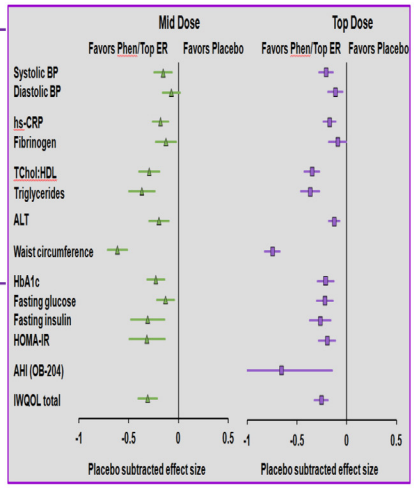
676명

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]

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

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].

*Am J Clin Nutr* 2012;95:297–308.

## Adverse Reactions Reported in ≥2% of Patients and More Frequently Than With Placebo (Year 1—Overall Study Population)

| System Organ Class<br>Preferred Term | Placebo (n=1561), % | Qsymia 3.75 mg/23 mg (n=240), % | Qsymia 7.5 mg/46 mg (n=498), % | Qsymia 15 mg/92 mg (n=1580), % |
|---|---|---|---|---|
| **Nervous System Disorders** | | | | |
| Paraesthesia | 1.9 | 4.2 | 13.7 | 19.9 |
| Headache | 9.3 | 10.4 | 7.0 | 10.6 |
| Dizziness | 3.4 | 2.9 | 7.2 | 8.6 |
| Dysgeusia (미각장애) | 1.1 | 1.3 | 7.4 | 9.4 |
| **Psychiatric Disorders** | | | | |
| Insomnia | 4.7 | 5.0 | 5.8 | 9.4 |
| Depression | 2.2 | 3.3 | 2.8 | 4.3 |
| Anxiety | 1.9 | 2.9 | 1.8 | 4.1 |
| **Gastrointestinal Disorders** | | | | |
| Constipation | 6.1 | 7.9 | 15.1 | 16.1 |
| Dry mouth | 2.8 | 6.7 | 13.5 | 19.1 |
| Nausea | 4.4 | 5.8 | 3.6 | 7.2 |
| Diarrhea | 4.9 | 5.0 | 6.4 | 5.6 |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue | 4.3 | 5.0 | 4.4 | 5.9 |
| **Eye Disorders** | | | | |
| Vision blurred | 3.5 | 6.3 | 4.0 | 5.4 |

The most common adverse reactions to Qsymia include paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth

# 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)

## Summary of Saxenda®

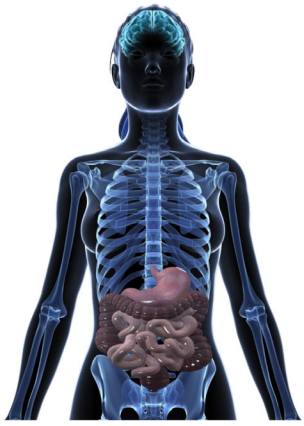
- Product: **Saxenda®** (liraglutide 3.0 mg)
  [Glucagon-like peptide-1 receptor agonist] (approved in 21st July 2017)
- Indication: Treatment of obesity (≥18yrs old)
  (29.9≥ BMI≥27 with comorbidities* or BMI≥30)
- Form: 6mg/mL in 3mL pre-filled pen (FlexTouch®)
- Administration: Any time once daily (min. 12hrs interval)
  Initiate with 0.6mg daily
  Weekly increase 0.6mg till reaching 3.0mg


Saxenda® product information submitted to MFDS, 2016

## Metabolic effects of GLP-1

**Appetite**[1]

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



**Glucose regulation**[2]
(Glucose-dependent)

- Insulin secretion
- Glucagon secretion

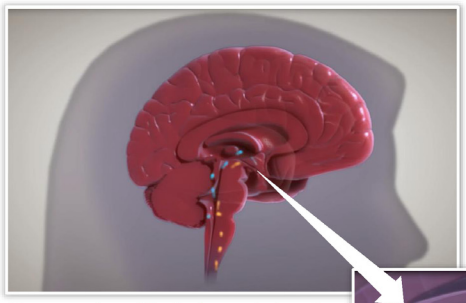
**Gastric effects**[3,4]

- Gastric acid
- Gastric emptying

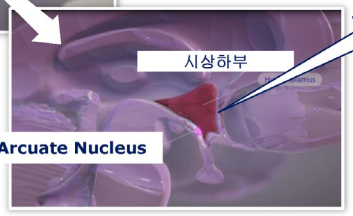
GLP-1 은 식욕을 생리적으로 조절하는 인자로, 포만감을 높이고 배고픔과 음식 섭취를 감소시킵니다.

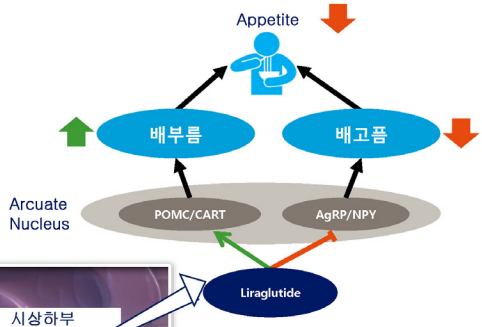
1. Flint *et al. J Clin Invest* 1998;101:515–20; 2. Nauck *et al. Diabetologia* 1993;36:741–4; 3. O'Halloran *et al. J Endocrinol* 1990;126:169–73; 4. Nauck *et al. Am J Physiol* 1997;273:E981–8

# 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

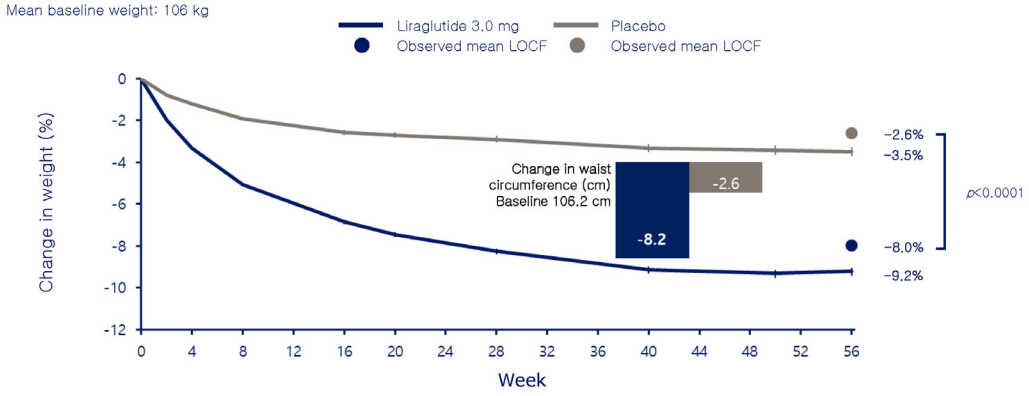
**SCALE Sleep Apnoea (3970)[4]**

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

# Change in body weight (%)




FAS, fasting visit data only. Line graphs are observed means (±SE). Statistical analysis is ANCOVA.
FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

Pi-Sunyer *et al. Diabetologia* 2014;57(Suppl. 1): Abstract 73-OR

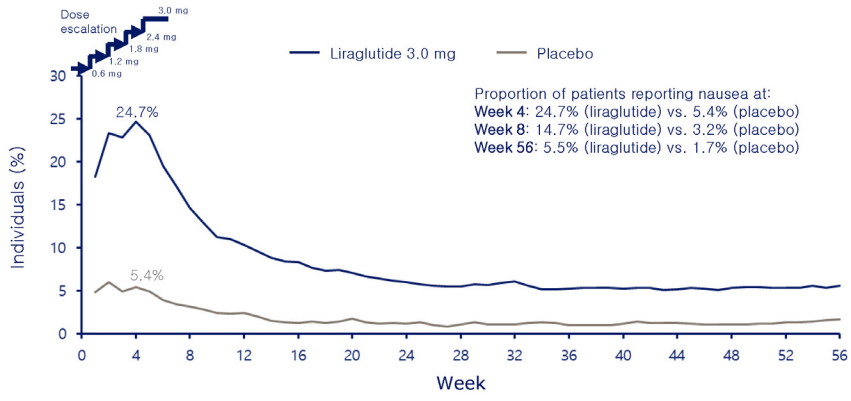
# Adverse effects

**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.[19]

# Proportion of individuals with nausea




Safety analysis set

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

# Summary of SAXENDA®


**4** SCALE clinical trials including **5358** patients[1]

*Strong weight loss efficacy– 9.2%▼BW*[2]

*Improved blood glucose level, BP & comorbidities*[2]

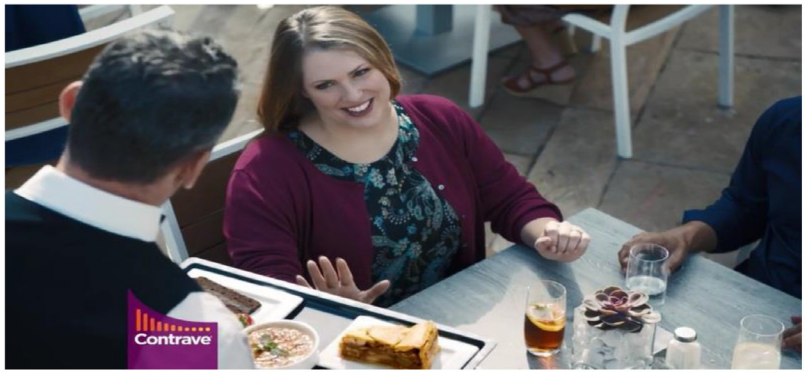
***4.5 yrs Proven CV Safety*** *– 22% risk reduction in CV death*[3]

1. Saxenda® [summary of product characteristics]. Bagsværd, Denmark: Novo Nordisk A/S; Mar-2015.
2. Pi-Sunyer et al. Int J Obes (Lond). 2013;37(11):1443-1451. 3. Marso SP et al. N Engl J Med 2016.

## 삭센다 임상적 적용과 장점

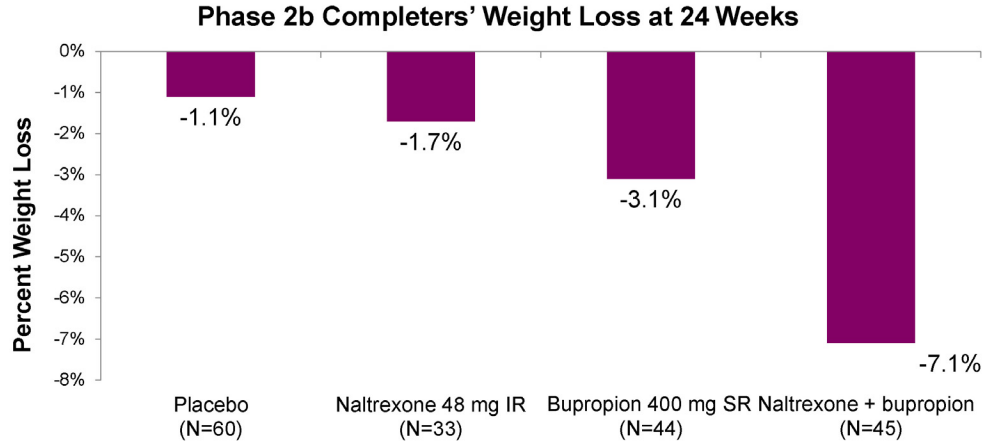
- 비향정신성약물
- 작용기전 : CNS, 위장관, 당뇨 치료
- 제한점 : 가격, 부작용
- Leader trial 심장 보호 효과가 있음

## Contrave


비향정 식욕억제제로 FDA·EMA 승인

# Naltrexone & Bupropion: Synergistic Pharmacology for Weight Loss



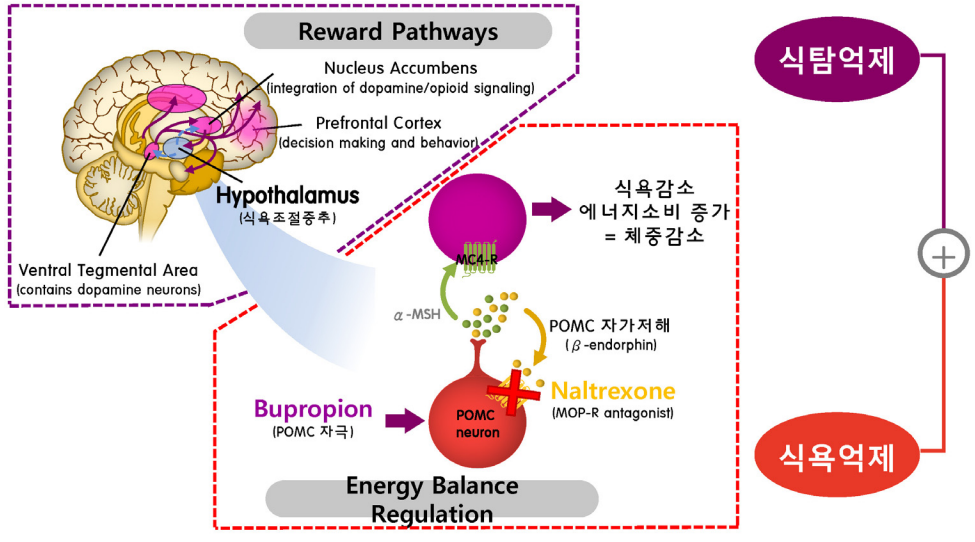

- Indicated for the treatment of alcohol and opioid dependence
- Indicated for the treatment of depression and smoking cessation

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

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



# 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**

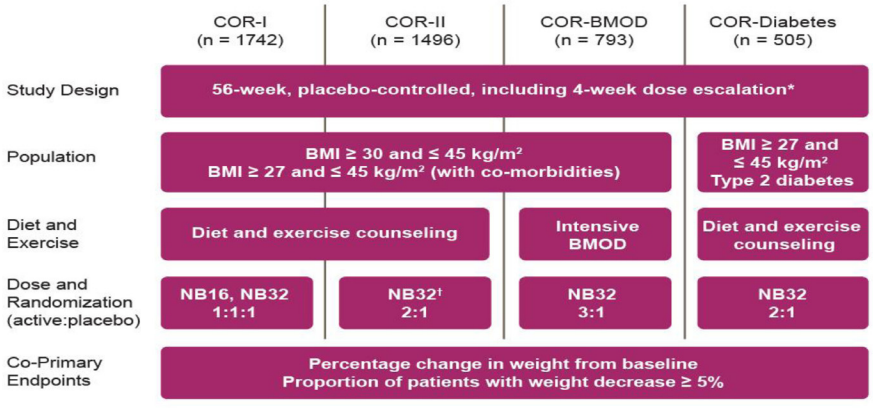
  - 1 Tablet : 8 mg naltrexone/ 90mg bupropion (2 tablets twice daily).

| 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

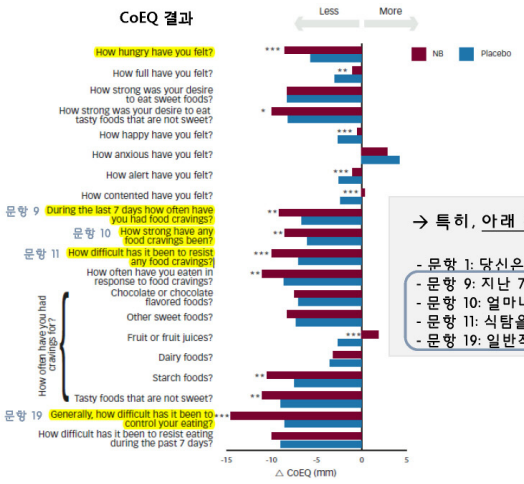



* For COR-II, full dose was reached by the start of week 5
† With exploration of NB48 in NB32 non-responders

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.

# Eating behavior에 대한 영향개선

→콘트라브는 섭식행동의 개선과 유의적인 관련성, 특히 식탐통제(Craving Control) 유의적 개선




→ 특히, 아래 문항에서 위약 대비 유의적인 개선이 관찰됨.

- 문항 1: 당신은 얼마나 배가 고픈가요?
- 문항 9: 지난 7일 동안, 당신은 얼마나 자주 식탐이 있었나요?
- 문항 10: 얼마나 강하게 식탐이 있었나요?
- 문항 11: 식탐을 견디는 것이 얼마나 어려웠나요?
- 문항 19: 일반적으로 당신의 섭식을 제어하는 것이 얼마나 어려웠나요?

Craving Control 관련

*p<0.05 vs. placebo, **p<0.01 vs. placebo, ***P<0.001 vs. placebo.

* CoEQ: 21 문항, 4가지 부척도로 구성. (Craving Control: 문항 9, 10, 11, 12, 19/ Positive Mood: 문항 5, 6, 7, 8/ Craving for Sweet: 문항 3, 13, 14, 15/ Craving for Savoury: 문항 4, 16, 17, 18)

- 대상: COR-연구(이중맹검, 무작위, 위약대조, 56주 투여) 4가지에 포함된 자 중 56주 투여 완료군: NB(1310명), 위약(763명)
- 방법: COR-연구에서는 2차 유효성 평가에서 식탐의 강도 및 유형에 대한 평가지표로 •CoEQ(Control of Eating Questionnaire)를 사용. CoEQ는 각 대상자들에서 지난 7일 동안의 경험에 따라 응답하도록 하였으며, 기저치/8주/16주/28주/56주 시, 측정했음. → COR-연구 4가지를 통합 분석.

1. Fujioka K et al., Presented at the American Diabetes Association (ADA) 73rd Scientific Sessions, June 21–25, 2013; . 2. M Dalton et al., Int J Obes 2017;41(8):1232-6.

# 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)† |

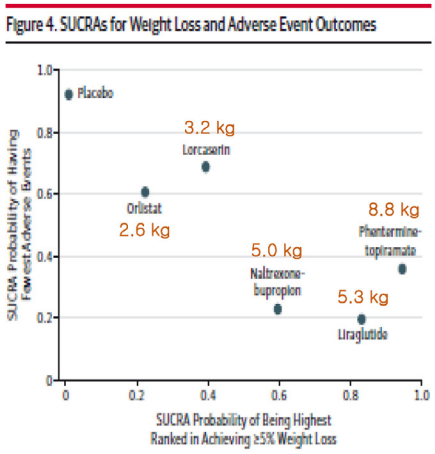
Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I) a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial Frank L Greenway etc., Lancet 2010; 376: 595–605

# 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.

# 비만약물 효과 비교



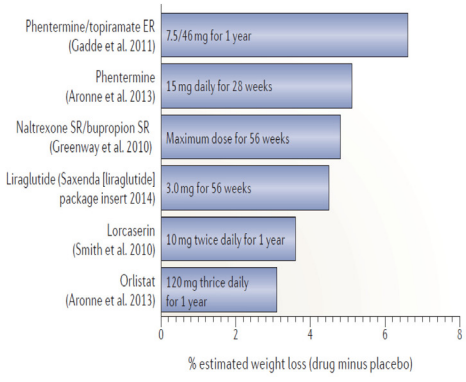




Figure 2 | **Efficacy of anti-obesity drugs.** The percentage estimated weight loss (drug minus placebo) for the six currently available anti-obesity drugs is depicted. ER, extended release; SR, sustained release.

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

Srivastava G, Apovian CM. Current pharmacotherapy for obesity. Nat Rev Endocrinol. 2018 Jan;14(1):12-24

# 사례

## 결론

- 식욕관련 신경전달물질 norepinephrine, serotonin, dopamine .
- 약물치료는 비만의 식사, 운동, 행동수정치료와 더불어 중요한 수단이다.
- 약물치료의 초기목표는 3개월동안 체중의 5-10%를 감량하는 것이다.
- 약물치료시 부작용과 특히 심혈관계통의 부작용에 대해서는 적극적 감시가 필요하다.
- 큐시미아, 콘트라브, 삭센다, FDA에 승인된 새로운 약물로 초기감량 및 유지요법으로 사용하고있다.