Korean Society for Health Promotion and Disease Prevention

2020년 대한임상건강증진학회 온라인 하계학술대회

2020.9.18(금)-19(토)

체중 조절 약물 Update

이 철 진 (좋은가정의원)

I. 총론 및 CASE
II. Qsymia
III. Sympathomimetics
IV. Liraglutide
V. Contrave
VI. 미래에 나올 약

CASE #1

- 20-30세 or 40-50세 여자 : 친구가 살 빠진 것을 보고 내원하게 됨
- 다이어트 경험+, YoYo+ : 약, 한약, 건기식, 헬스클럽, 유행하는 다이어트

- BMI 23-25, 27-30, 체지방율 32%-40%
- 목표 : 45kg-50kg

- Hx : 대사이상질환, 생리통, 두통, 관절통, 가족력
- 생활습관 : 술, 믹스커피, 콜라 주스, 과자, 빵, 야식, 스트레스 폭식, 생리 전후 폭식
  전 별로 잘 안 먹어요!

Tx :

➔1) 식단조절 및 생활습관조절 처방 : 뭘 먹어라 or 먹지 마라

➔2) 어떤 약을 처방할까?

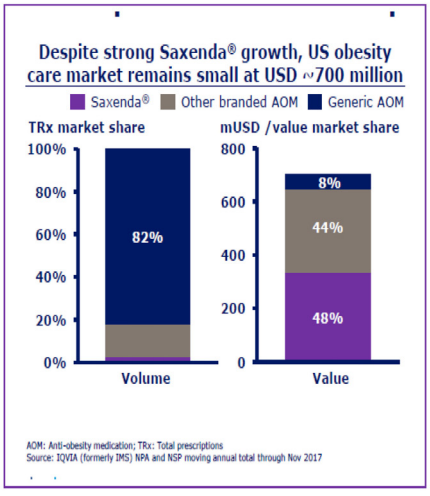
Short term : Phentermine or Phendimetrazine
Long term : Orlistat, Liraglutide, Contrave, Qsymia
Off-Label : Fluoxetine, Topiramate, 보조제

성분별 비만 시장 추이

[처방액(단위 : 백만원)]

[처방량(단위 : 천)]

성분	2015년	2016년	2017년	2018년	2019년	전년대비	CAGR	2015년	2016년	2017년	2018년	2019년	전년대비	CAGR



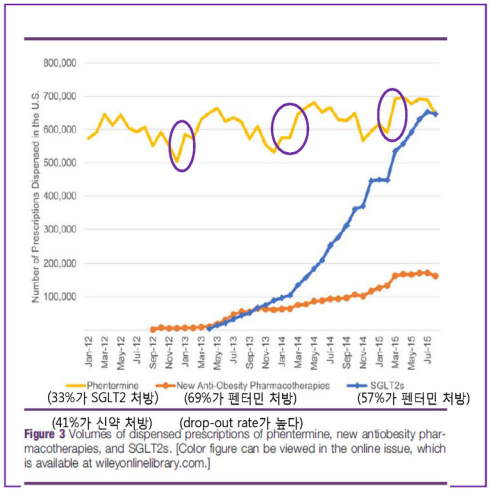
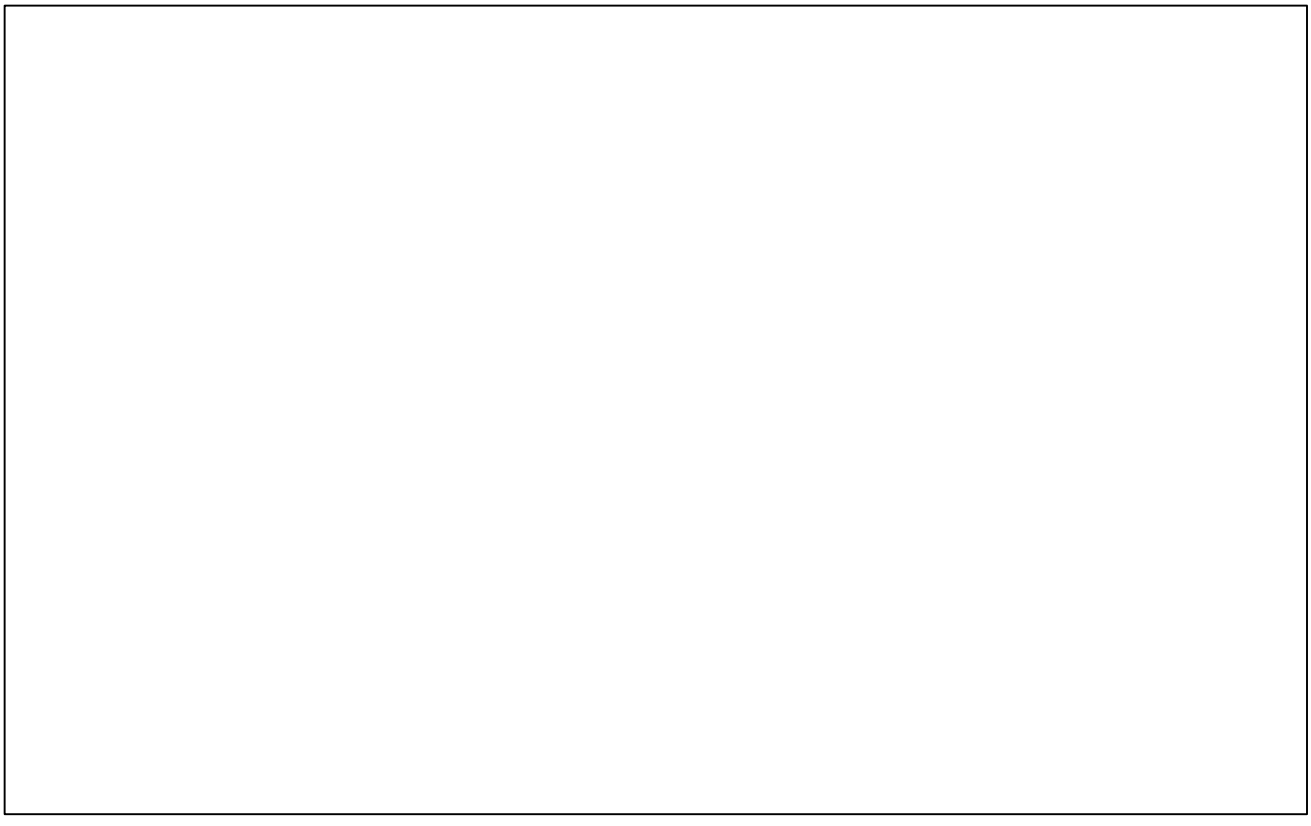


Figure 3 Volumes of dispensed prescriptions of phentermine, new antiobesity pharmacotherapies, and SGLT2s. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Obesity | VOLUME 24 | NUMBER 9 | SEPTEMBER 2016

2018 Novo Nordisk IR자료



동기부여

CASE #6, F/27, BMI 27, 70kg

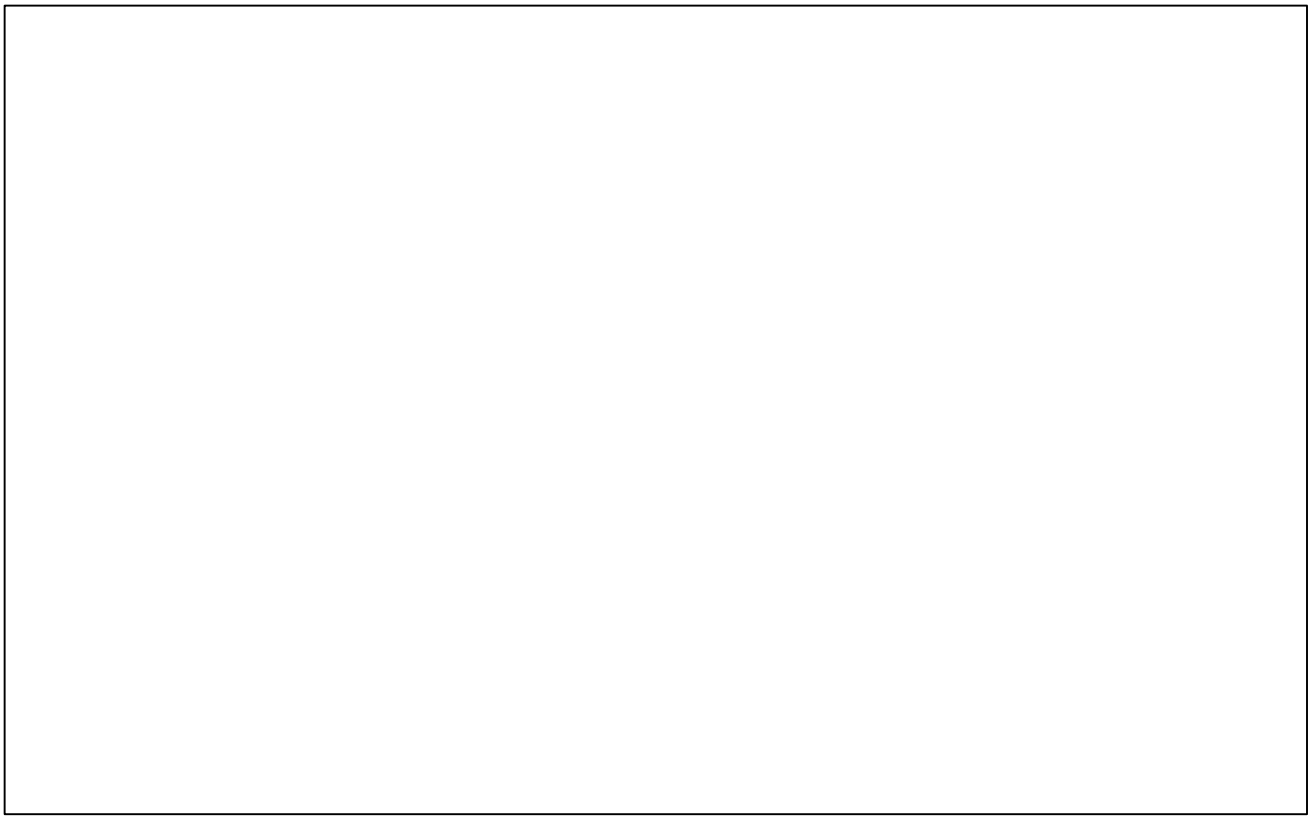
- **남자 친구 생김**(여행, 비키니)

70.0 -> 67.1 - 65.7 - 65.1 - 64.3 - 62.3 - 61.9 - 60.5
59.3 - 58.7 - 58.4 - 57.6 - 56.2 - 56.0 - 54.8- 54.2
53.6
생리전 라면 땡긴다.
남자친구 때문 6개월전 생김
운동 : 스쿼트 100개 3세트 4일되었다

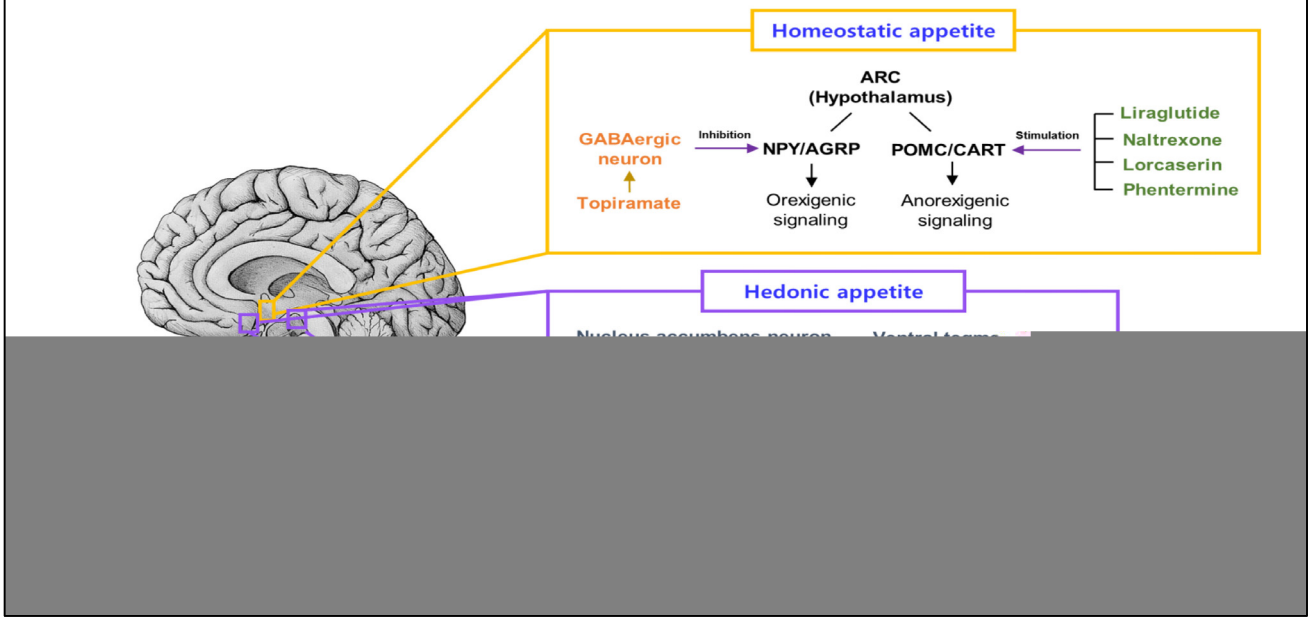
CASE #7, F/27, BMI 26, 68kg

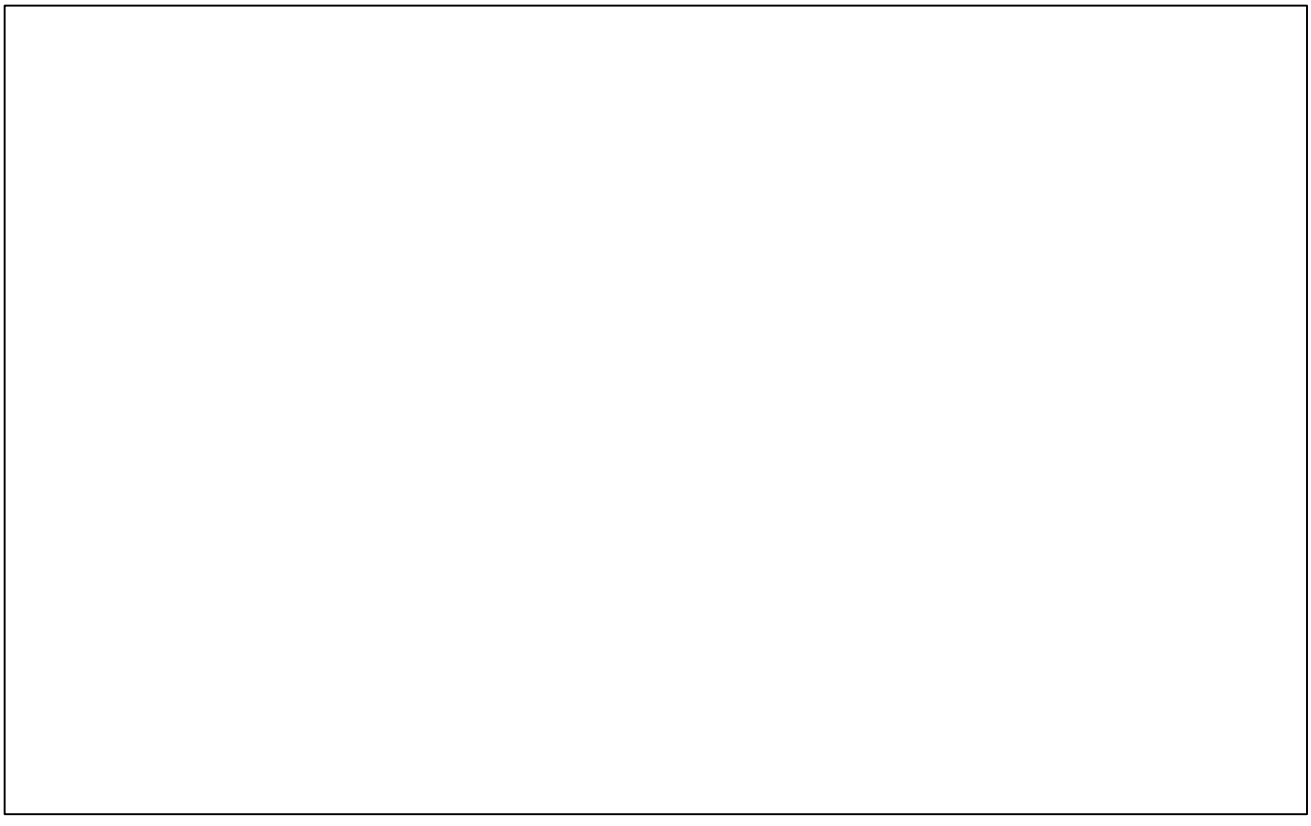
- **결혼 예정**(웨딩 촬영, 결혼식)

68.7 - 66.5 - 64.8 - 64.4 - 63.5 - 62.8 - 62.4 - 61.5
61.5 - 60.5 - 59.3 - 58.9 - 57.9 - 56.9 - 56.2 - 56.6
55.2
결혼계획중,
4월 4일 웨딩촬영 강남
결혼식 7월 12일



작용기전


Homeostatic appetite
ARC
(Hypothalamus)
GABAergic
neuron
Inhibition
NPY/AGRP
POMC/CART
Stimulation
Liraglutide
Naltrexone
Lorcaserin
Phentermine
Topiramate
Orexigenic
signaling
Anorexigenic
signaling
Hedonic appetite



I. 큐시미아 Phentermine/Topiramate ER

1. 처방 용이

2. 가장 강력한 체중감소 효과

3. 장기 처방 가능, 안전성

1. 처방용이

Phentermine
Hydrochloride

Topiramate

Phentermine/Topiramate extended release

Phentermine (Maximum approved dose, 30 mg)

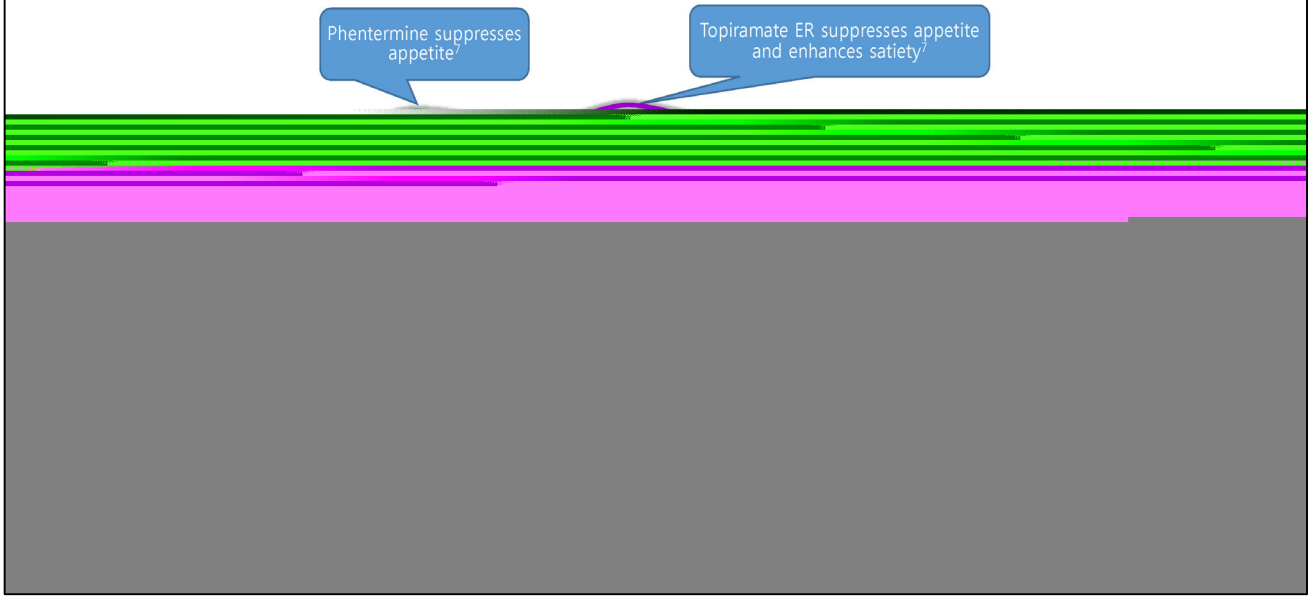
30

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**

큐시미아 작용기전



2. 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	-3.5 -9.4
	CONQUER	Qsymia Mid Qsymia Top Placebo	488 981 979	-6.6 -8.6 -

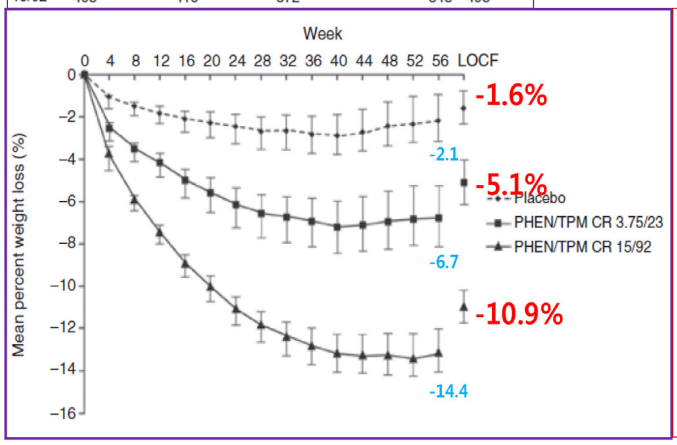
EQUIP

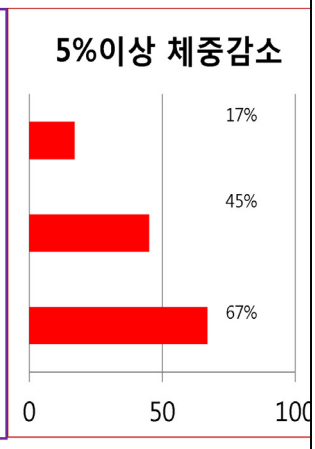
1267명, BMI 350이상

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

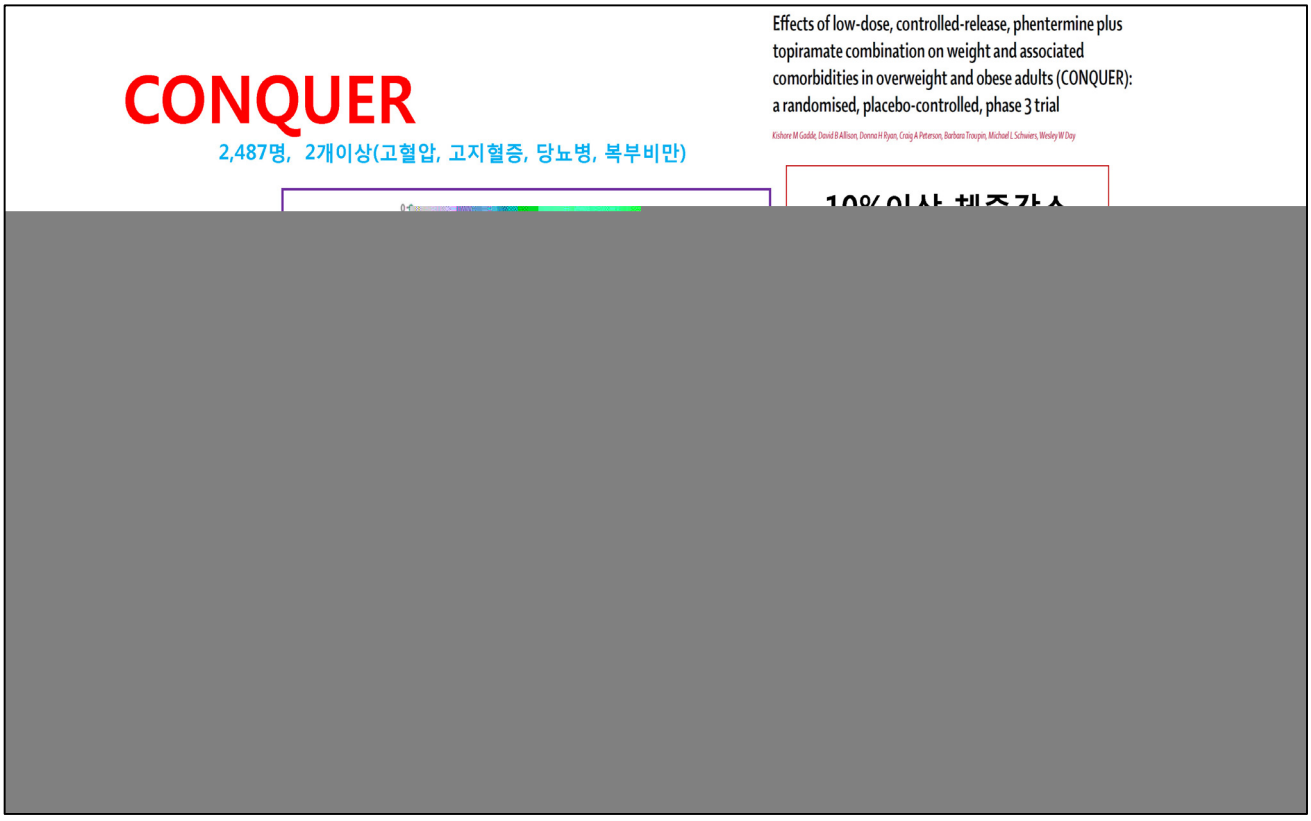
David B. Allison[1,2], Kishore M. Gadde[3], William Timothy Garvey[2,4], Craig A. Peterson[2], Michael L. Schwiers[5], Thomas Najarian[5], Peter Y. Tam[5], Barbara Troupin[5] and Wesley W. Day[5]

n					
Placebo	498	362	303	279	498
3.75/23	234	190	165	149	234
15/92	498	416	372	348	498





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

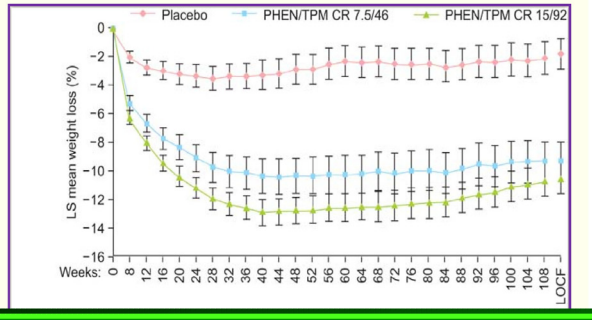

CONQUER
2,487명, 2개이상(고혈압, 고지혈증, 당뇨병, 복부비만)
Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial
Kishore M Gadde, David B Allison, Donna H Ryan, Craig A Peterson, Barbara Troupin, Michael L Schwiers, Wesley W Day

SEQUEL

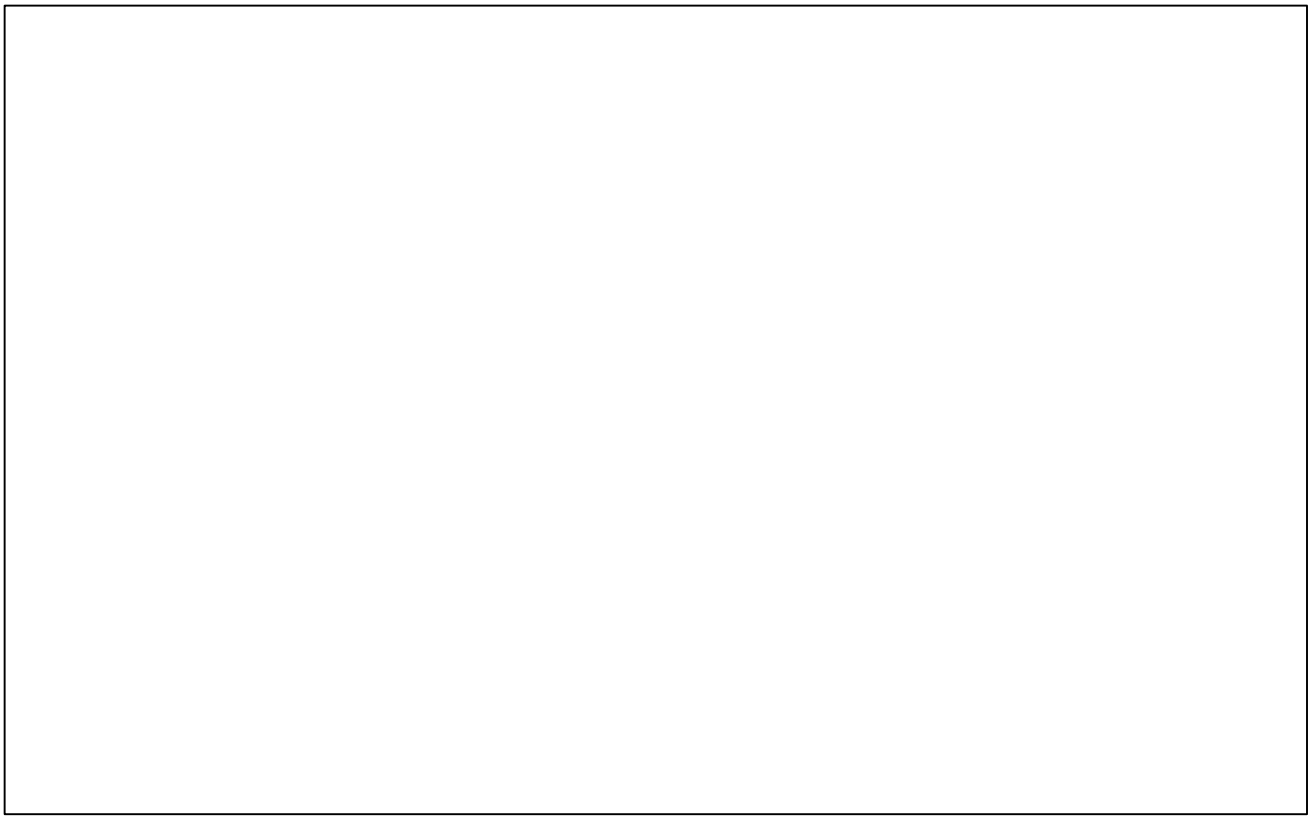
676명

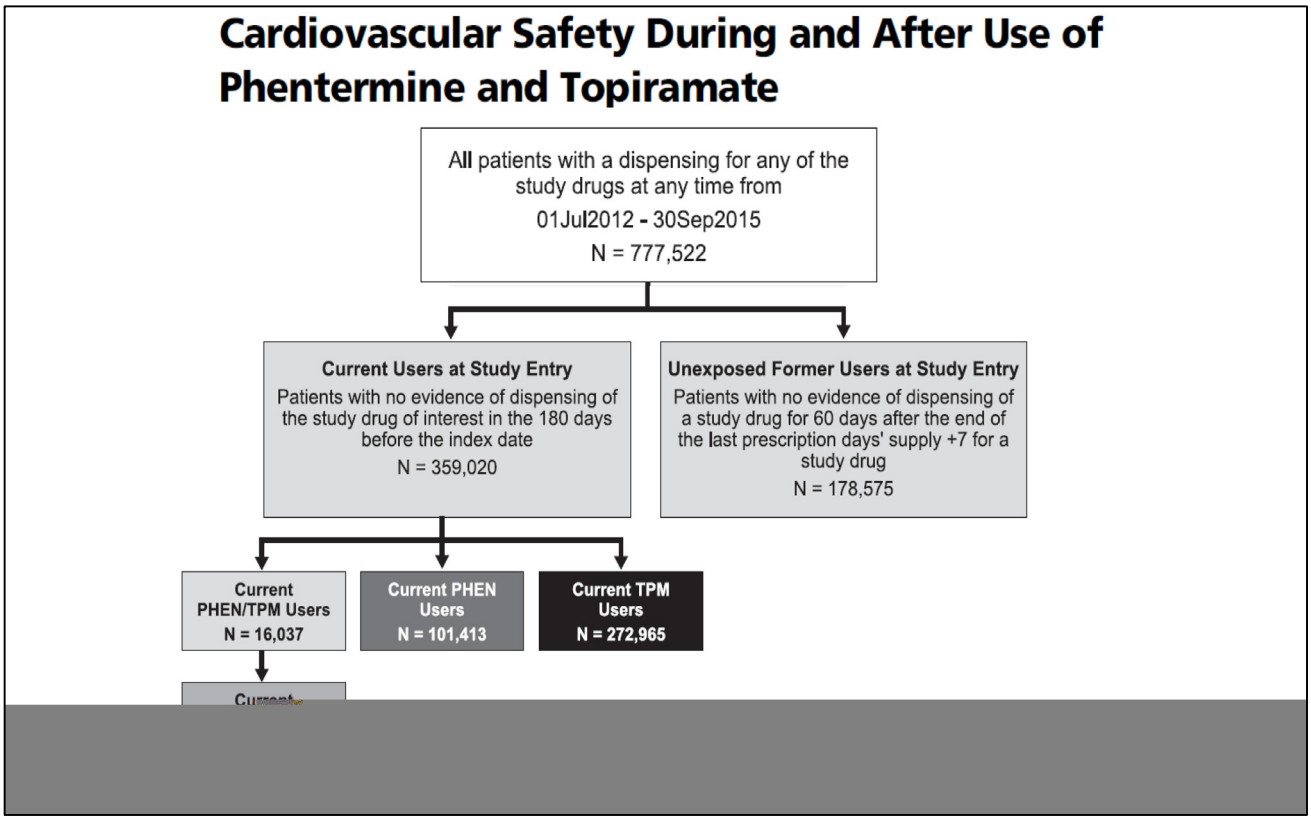
Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study[1-3]

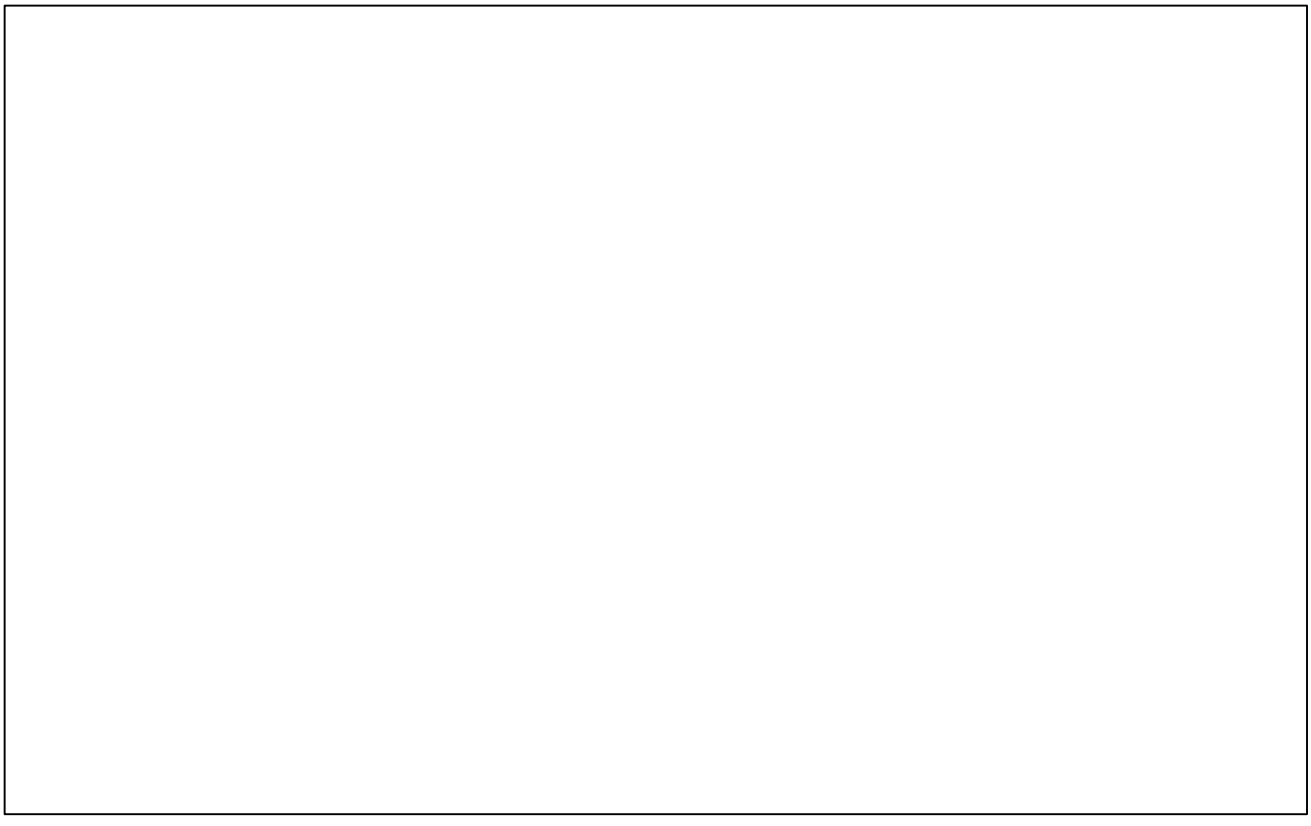
Figure 3

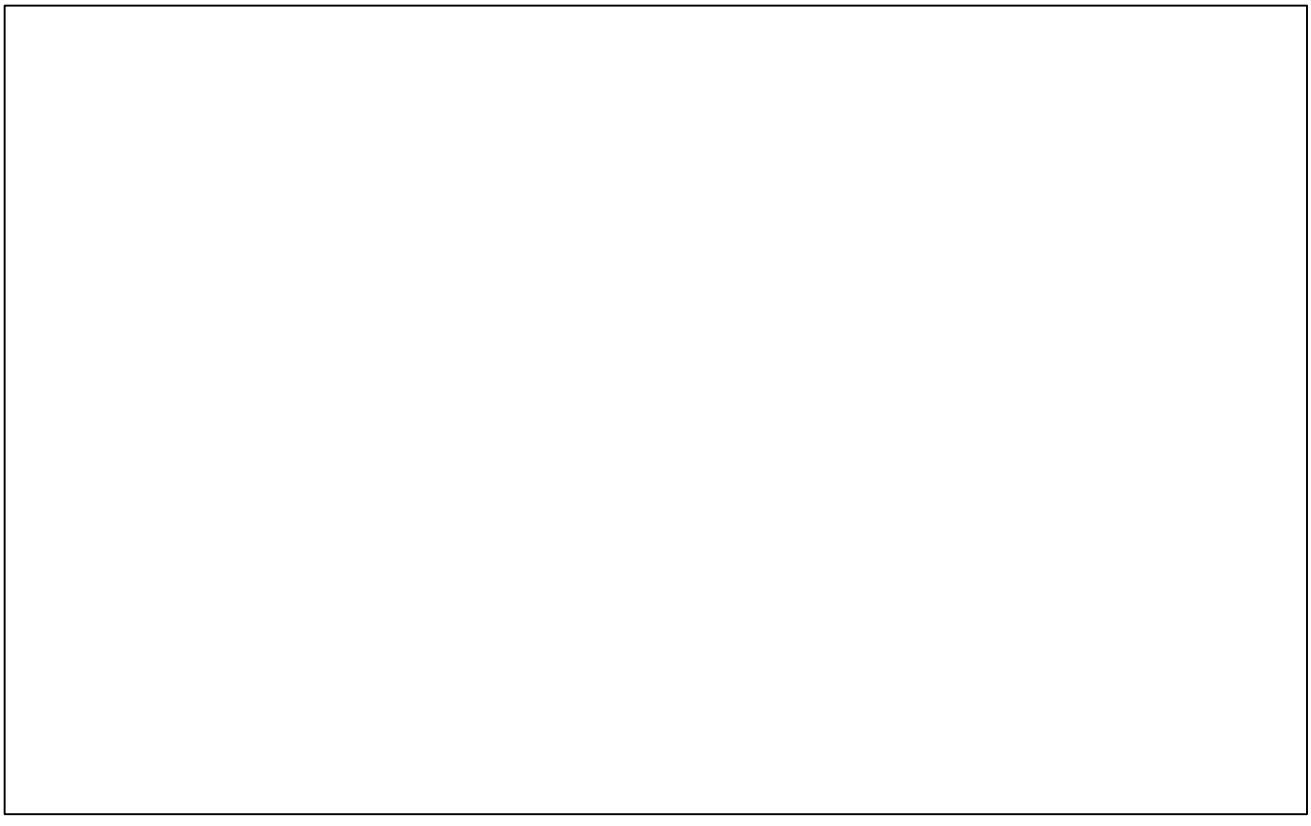


심혈관질환 위험인자 개선 및




Cardiovascular Safety During and After Use of Phentermine and Topiramate
All patients with a dispensing for any of the study drugs at any time from
01Jul2012 - 30Sep2015
N = 777,522
Current Users at Study Entry
Patients with no evidence of dispensing of the study drug of interest in the 180 days before the index date
N = 359,020
Unexposed Former Users at Study Entry
Patients with no evidence of dispensing of a study drug for 60 days after the end of the last prescription days' supply +7 for a study drug
N = 178,575
Current PHEN/TPM Users
N = 16,037
Current PHEN Users
N = 101,413
Current TPM Users
N = 272,965





Phentermine 장기 연구

TABLE 18.1
Longer-Term, Placebo-Controlled Studies with Phentermine or Diethylpropion

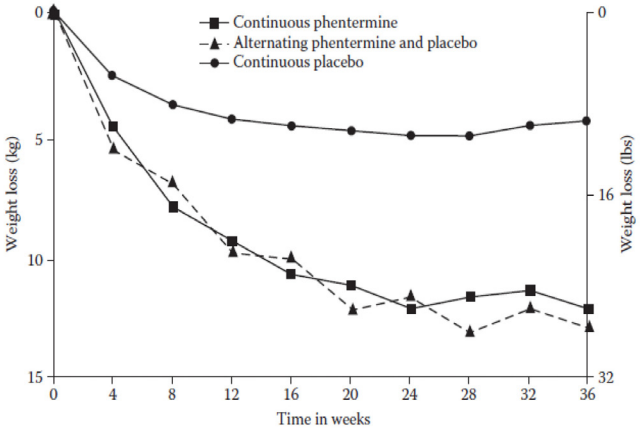


FIGURE 18.2 Mean weight loss over 36 weeks with placebo, continuous phentermine, and intermittent phentermine (1 month phentermine alternating with 1 month placebo). (From Munro JF et al., *Br. Med. J.* 1, 352–356, 1968.)

Safety and Effectiveness of Longer-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record Cohort

13,792명, 3개월미만 사용군(6764명)을 기준으로 6개월, 1년, 2년뒤 비교

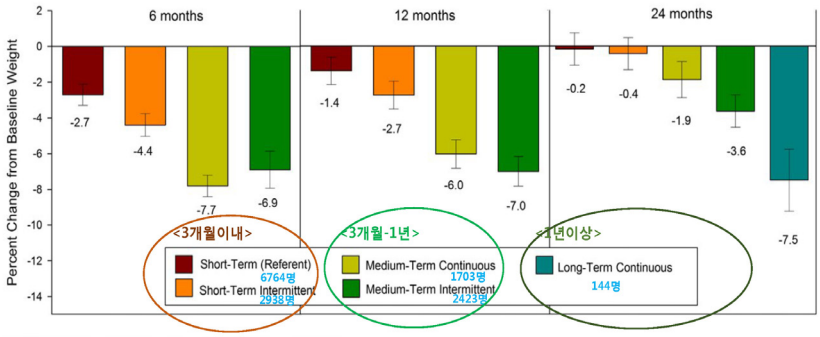


Figure 2 Estimated percent weight loss at 6 months and 1 and 2 years after phentermine initiation; results from multivariable linear models. Estimates at each time point are from separate multivariable linear models, and *n* (%) by group over follow-up is presented in Table 2. Note that because real clinical follow-up does not occur at exact 6-month intervals, weights were drawn from an acceptable time window of outpatient visits around each time point of interest, as outlined in *Methods*. Estimates for the referent group (on-label continuous) were based on the y-intercept of multivariable models in the case in which all covariates are set to referent. Estimates for comparison groups were generated by summing the intercept weight loss and the additional change in weight by group at each time point. Error bars represent 95% CI for each estimate.

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Safety and Effectiveness of Longer-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record

Safety and Effectiveness of Longer-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record Cohort

13,792명, 3개월미만 사용군(6764명)을 기준으로 6개월, 1년, 2년뒤 비교

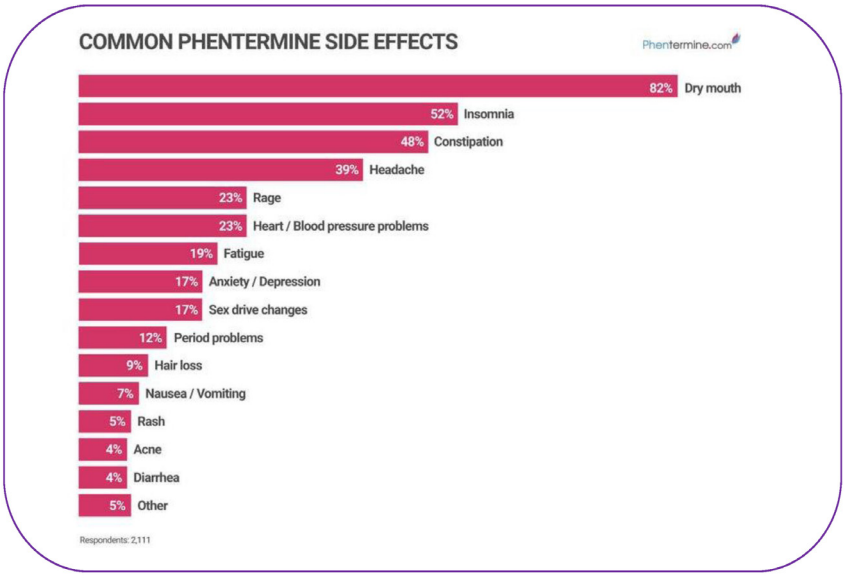
TABLE 5 Results from multivariable Cox models[a]: hazard ratio for composite outcome of incident myocardial infarction, stroke, CVD intervention, or death up to 3 years after phentermine initiation

	Hazard ratio	CI[b]
Short-term (referent)	Reference	
Short-term intermittent	0.74	0.29-1.91
Medium-term intermittent	0.50	0.14-1.74
Medium & long-term continuous combined[c]	1.58	0.69-3.63

[a]Models include phentermine exposure as time-varying covariate as well as gender, race and ethnicity, smoking, diabetes, hypertension, baseline BMI, average medication strength, year of original prescription, and site.
[b]$P = 0.30$ for examining differences between groups.
[c]There were no events in long-term continuous subgroup; therefore, to allow this group to contribute person-time to the models, it was grouped with the medium-term continuous exposure c...

3. 제한점

Phentermine 부작용



<대한비만학회지 제14 권 제3 호 2005>

1. 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]

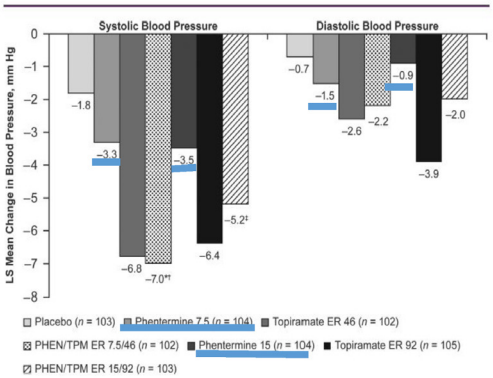


FIGURE 3 LS mean change in systolic and diastolic blood pressure from baseline to week 28 in the ITT-LOCF population. *$P = 0.0004$ vs. placebo; †$P = 0.0108$ vs. phentermine 7.5; ‡$P = 0.0224$ vs. placebo. ITT, intention-to-treat; LOCF, last observation carried forward; LS, least squares; PHEN/TPM ER 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 (11.68)

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.

Obesity | VOLUME 21 | NUMBER 11 | NOVEMBER 2013

2. 신경정신
- ①Addiction

ORIGINAL ARTICLE

Addiction potential of phentermine prescribed during long-term treatment of obesity

EJ Hendricks[1], M Srisurapanont[2], SL Schmidt[3], M Haggard[1], S Souter[1], CL Mitchell[1], DG De Marco[1], MJ Hendricks[1], Y Istratiy[1] and FL Greenway[4]

SUBJECTS: 269 obese, overweight or formerly obese subjects (age: 20–88 years, BMI: 21–74 kg m^{-2}) treated with phentermine long-term (LTP, $N = 117$), 1.1–21.1 years, or short-term (ATP, $N = 152$), 4–22 days, with phentermine doses of 18.75–112.5 (LTP) and 15–93.75 (ATP) mg per day.
MEASUREMENTS: Module K of the Mini International Neuropsychiatric Interview modified for phentermine (MINI-SUD), Severity of Dependence Scale (SDS), 45-item Cocaine Craving Questionnaire-NOW (CCQ-NOW) modified for phentermine (PCQ-NOW), and Amphetamine Withdrawal Questionnaire (AWQ) modified for phentermine (PWQ).

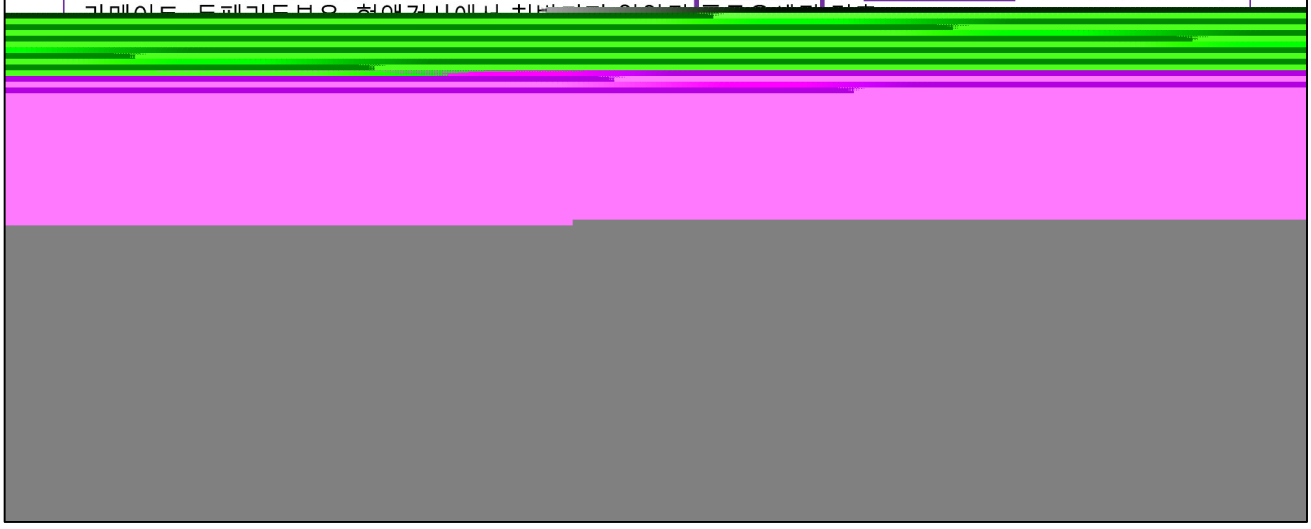
3. 사망사례

Acute cardiac death associated with polypharmacy during use of anti-obesity drug

Tae Hoon Kang[1], AiHua Zhang[1], Hyoung Joong Kim[2], Seong Ho Yoo[1], Chung Hee Sun[2] and Soong Deok Lee[1]

[1]Department of Forensic Medicine and Institute of Forensic Medicine, Seoul National University Medical College; and [2]National Institute of Scientific Investigation, Korea

1. 22세 여성, 수면중 호흡곤란 → ER → 사망, 사망 당일까지 17일동안 펜디메트라진, 이뇨제, 발륨, 토피



3. 사망사례

Ornella Leone et al ; Sudden Cardiac Death

1. 37/M, 9개월동안 펜디메트라진 복용(180-210mg) + BDZ, thyroid H, diuretics → 수면 중 사망
2. 42/F, 5년 펜디메트라진 복용(100-225mg) + fluoxetine bupropion, BDZ ....
3. 28/F, 5개월 펜디메트라진 복용(120mg) + fluoxetine, BDZ, ...

Pathology : LVH, small vessel disease, toxic myocarditis, scarring

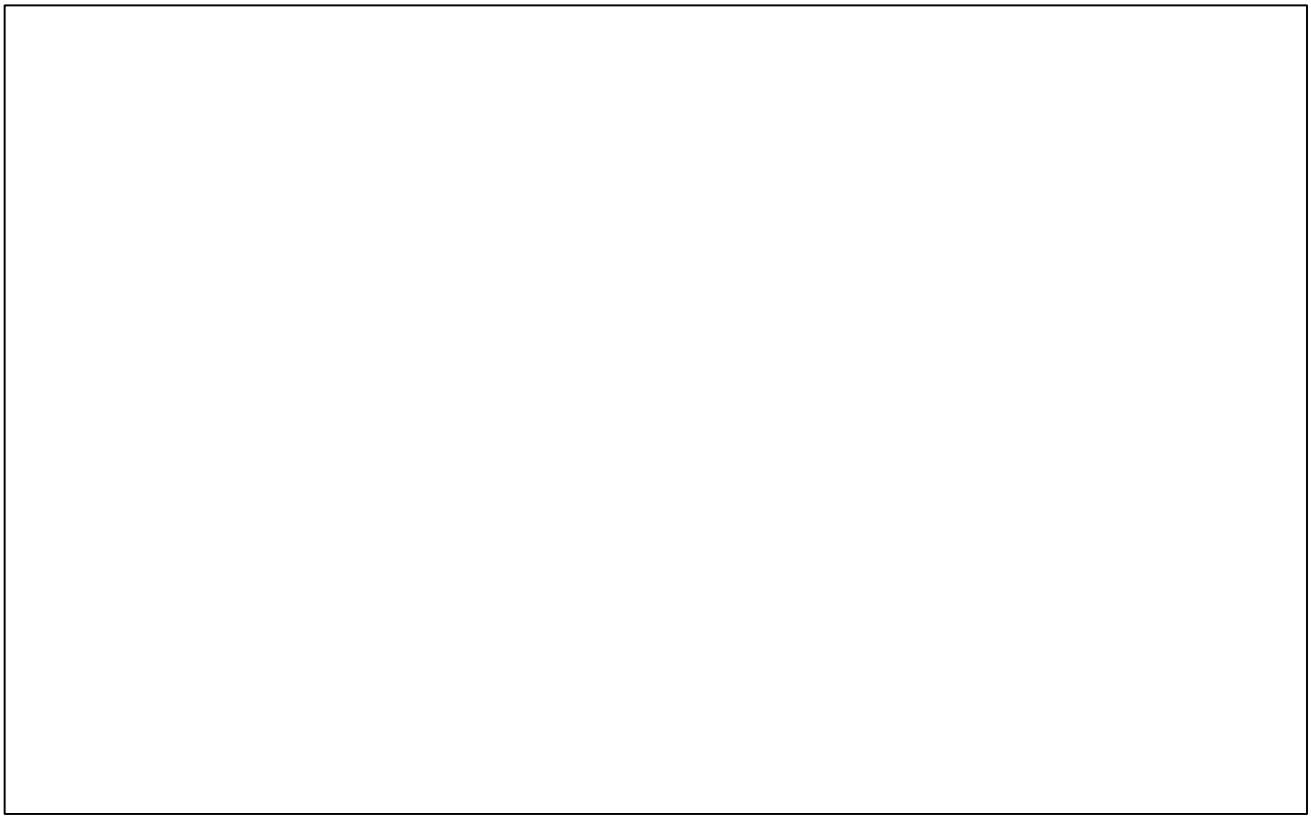
Hum Pathol. 2017 Nov;69:101-109.

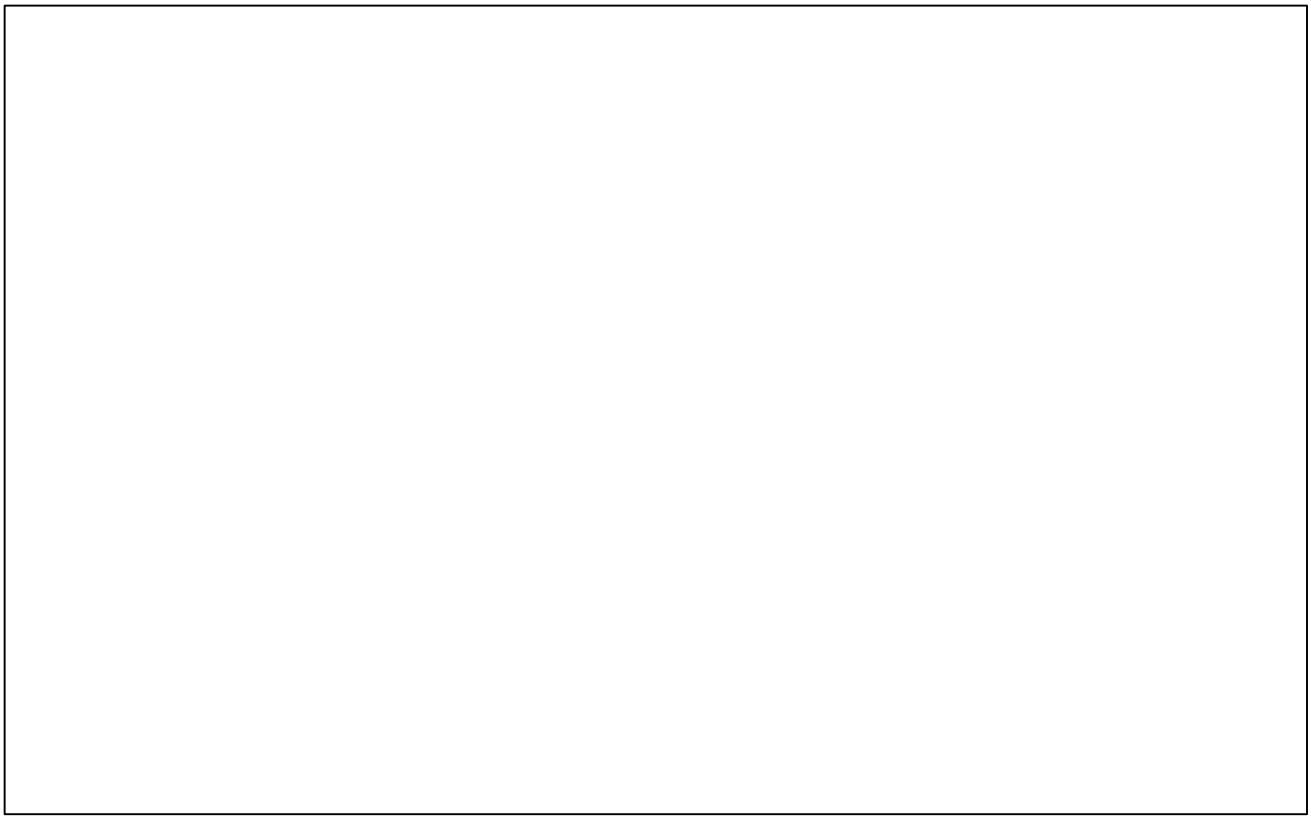
III. Liraglutide

1. 작용기전 : CNS, 위장관, 당뇨 치료

2. SCALE study

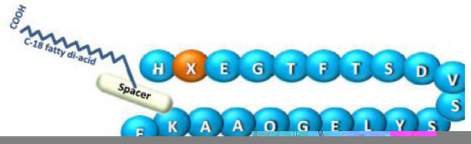
3. 제한점 : 가격, 부작용





1. 작용기전

Diabesity = Obesity + Diabetes

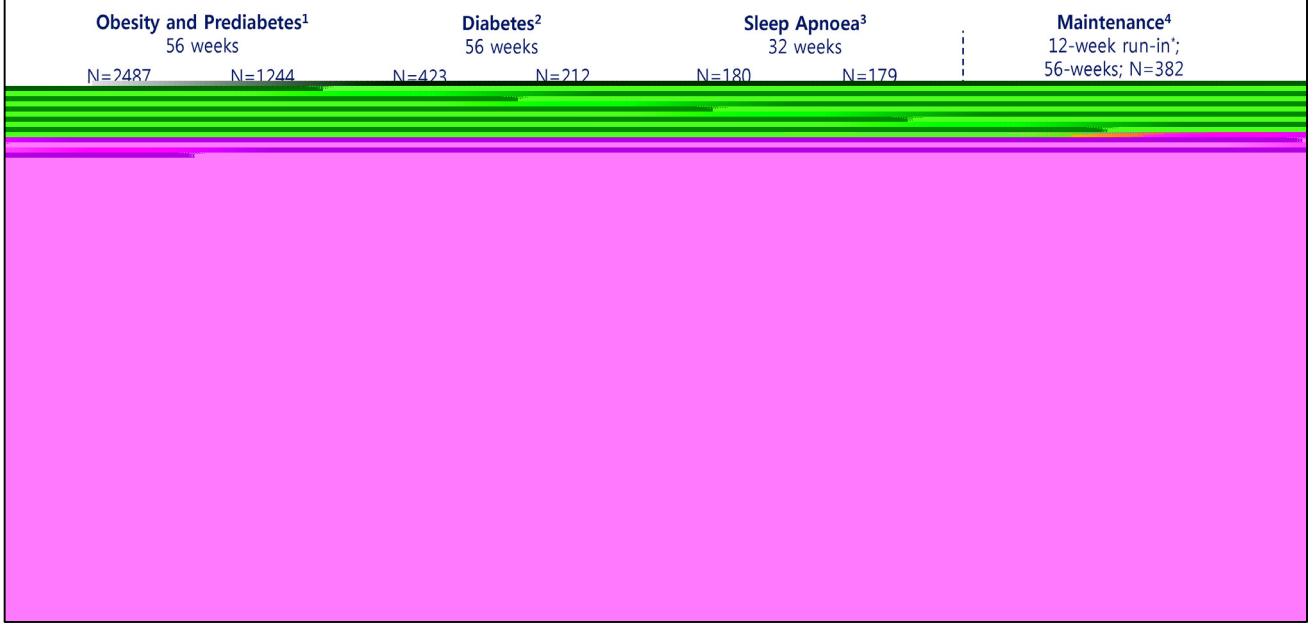


16.2% weight reduction with the highest semaglutide dose in phase 2 obesity trial

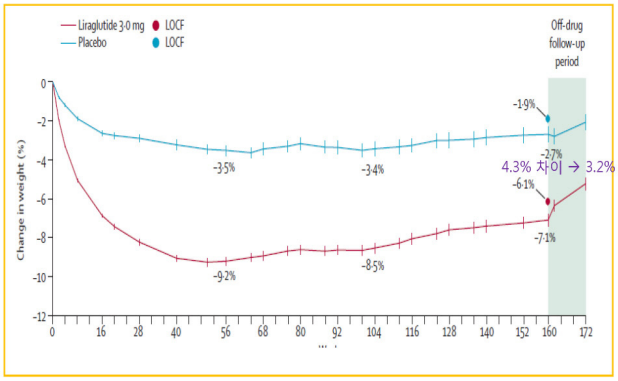
Change in body weight

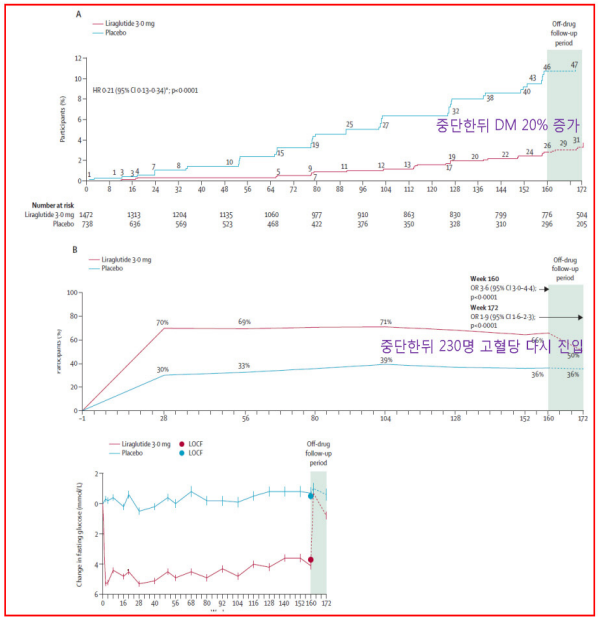
sema 0.05 mg
sema 0.1 mg
sema 0.2 mg
sema 0.3 mg

Weight loss across SCALE trials



3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial 2254명(1505명, 749명)



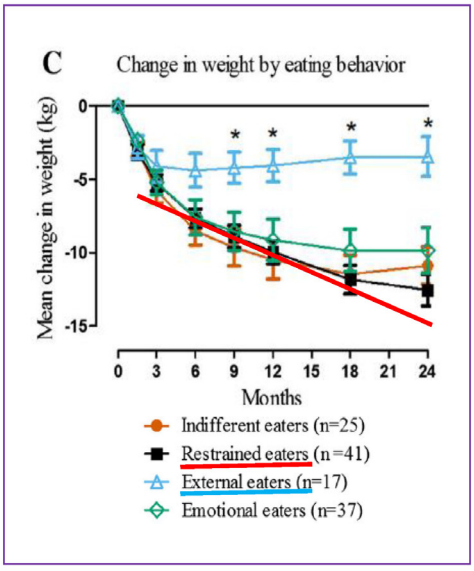


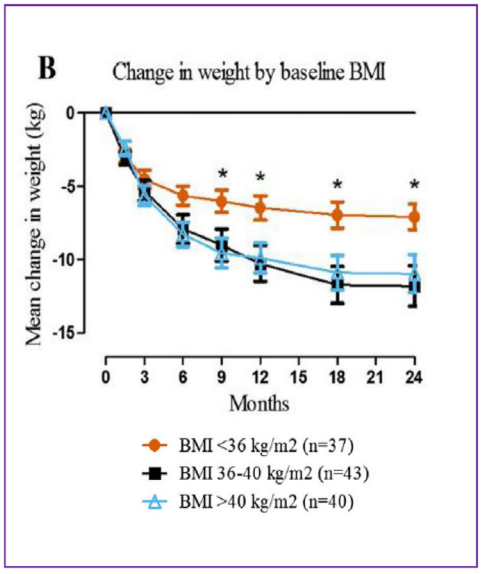
GB related events : 74명(5%) vs 13명(2%) d/t GB emptying ??
Pancreatitis : 10명(0.7%) vs 2명(0.3%)
Breast malignant and premalignant neoplasm : 10명 vs 0명
Suicidal ideation : 8명 vs 1명

www.thelancet.com **Published online February 22, 2017**

Effects of liraglutide on weight, satiation, and gastric

The effects of GLP-1 analogues in obese, insulin-using type 2 diabetes in relation to eating behaviour <151명, 2년>





Int J Clin Pharm (2016) 38:144–151

ORIGINAL ARTICLE

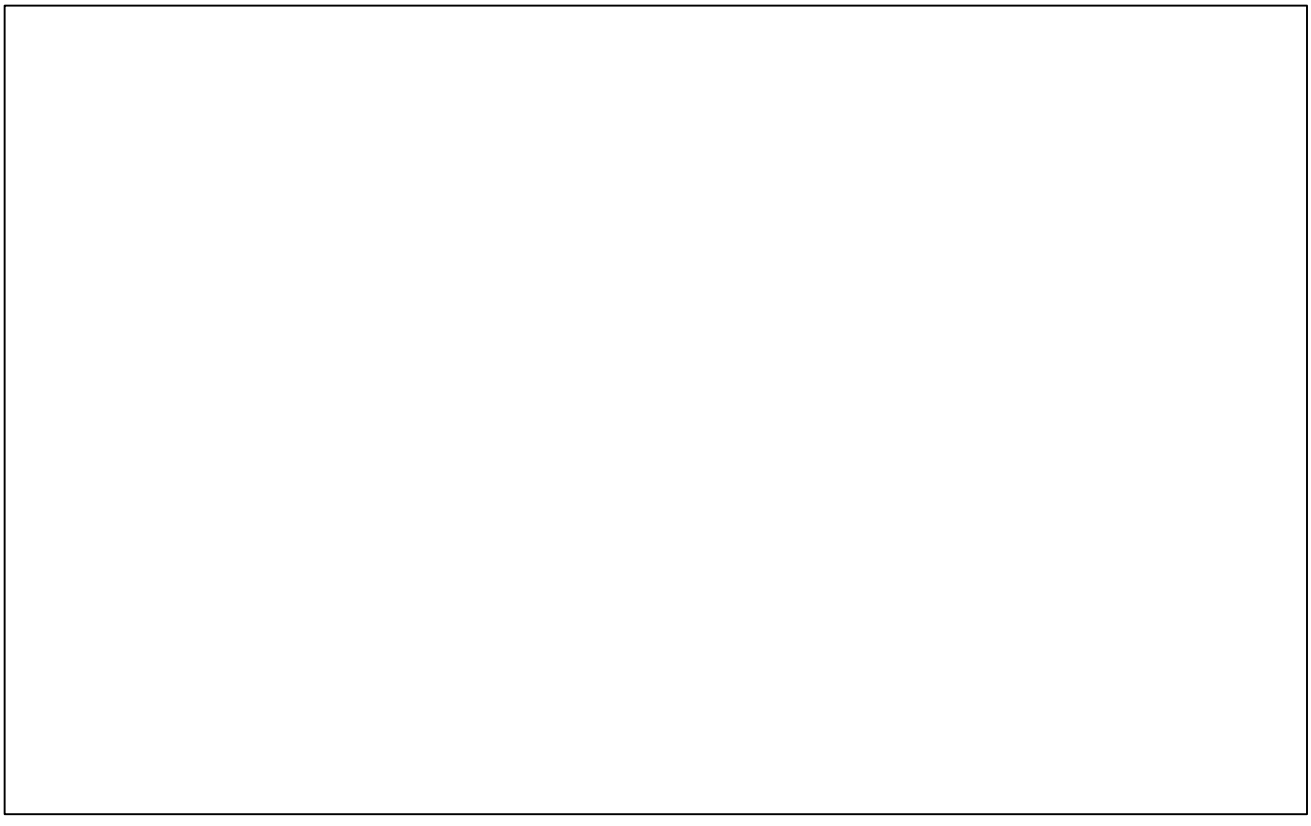
Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin during maintenance of

IV. Contrave(Naltrexone/Bupropion)

1. 식탐억제

2. 임상 : 음식 중독, 우울증, 음주 흡연 환자

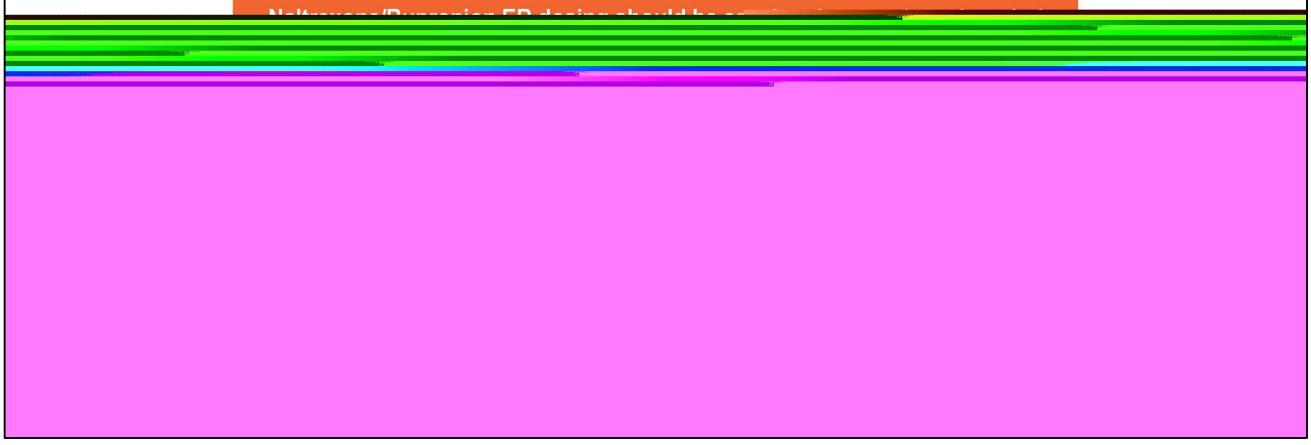
3. 제한점 : Nausea



3. 제한점

사용방법 주의점

- 다른 식욕억제제와 병용 금기
- 금기 : 조절 안된 고혈압, 경련, Bulimia or Anorexia Nervosa, 임신 등

› 용량, 용법

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