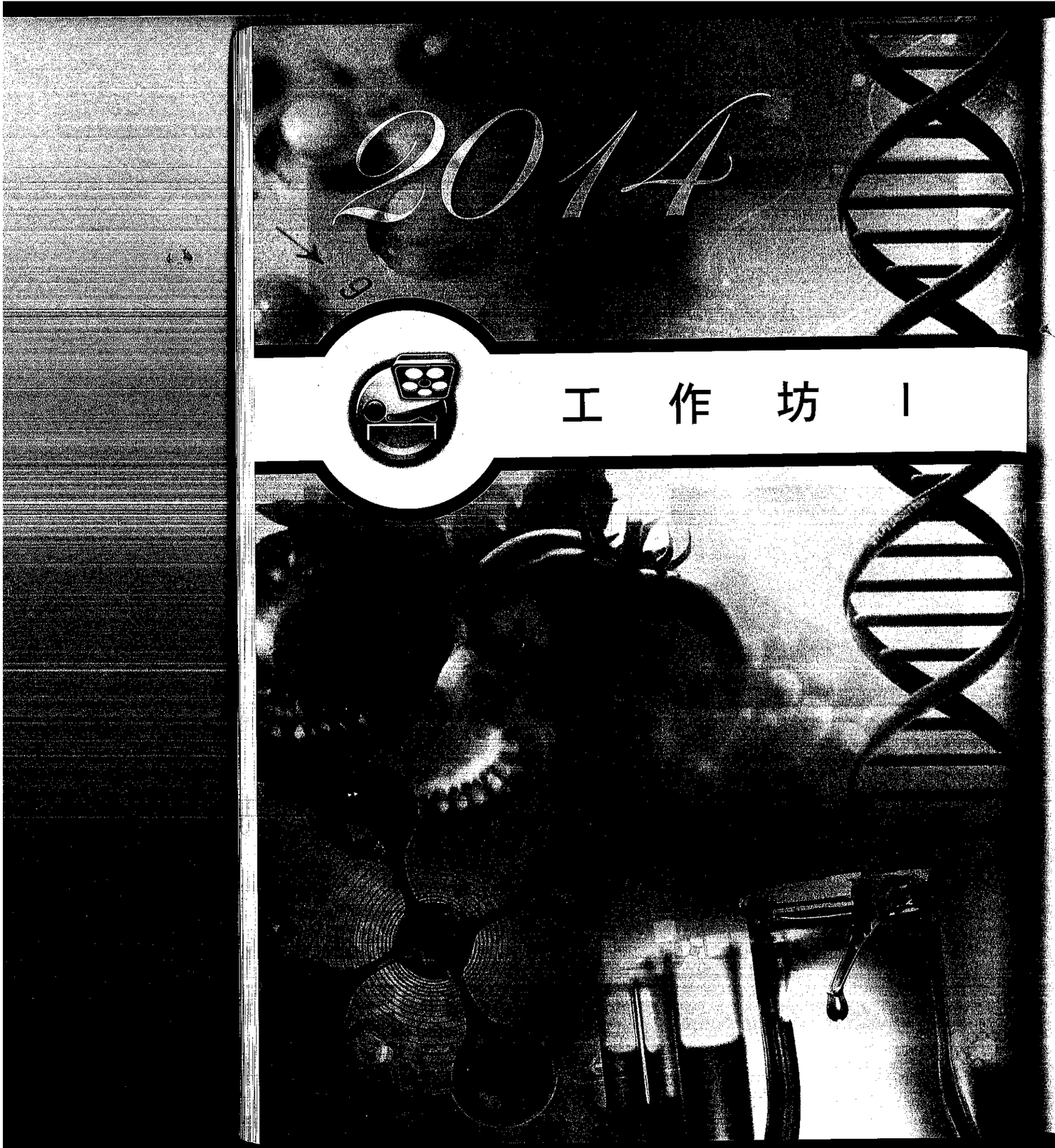


林文元 Wen-Yuan Lin

主要學歷：

學校名稱	國別	主修學門系所	學位	起訖年月 (西元年 / 月)
中國醫藥大學	中華民國	醫學系	學 士	1989 / 9 至 1996 / 6
台灣大學公共衛生學院	中華民國	預防醫學研究所	碩 士	2001 / 9 至 2003 / 6
中國醫藥大學	中華民國	臨床醫學研究所	博 士	2006 / 9 至 2010 / 6

現職及與專長相關之經歷：

服 務 機 構 及 單 位	職 稱	起迄年月
現任：中國醫藥大學附設醫院家庭醫學科	主治醫師	2002 / 7 迄今
中國醫藥大學醫學系	教授	2013 / 8 迄今
台大醫院家庭醫學部	兼任主治醫師	2002 / 7 迄今
曾任：國軍軍管區八零三一醫務所	醫官	1996 / 7 至 1998/6
台大醫院家庭醫學部	住院醫師	1998 / 7 至 2001/6
恩主公醫院家庭醫學科	主治醫師	2001 / 7 至 2002/6
中國醫藥大學醫學系	講師	2004 / 8 至 2007/1
中國醫藥大學醫學系	助理教授	2007 / 2 至 2010/1
中國醫藥大學醫學系	副教授	2010 / 2 至 2013/7
美國哥倫比亞大學	訪問學者	2008 / 8 至 2009/8
美國紐約 Saint Luke's-Roosevelt Hospital Center	研究員	2008 / 8 至 2009/8

專長：

家庭醫學	緩和醫學	肥胖醫學	預防醫學	老年醫學	旅遊醫學

學會：

台灣肥胖醫學會 秘書長、台灣醫用營養醫學會 理事，台灣國際醫療保健學會 常務理事、台灣動物輔助活動及治療協會 (台灣狗醫生協會) 理事長、台灣中國醫藥大學醫學系系友會 監事、台灣老年學暨老年醫學會 副秘書長

專科醫師：

台灣家庭醫學專科醫師、台灣肥胖醫學專科醫師、台灣老年醫學專科醫師、台灣安寧緩和醫學專科醫師、台灣青少年醫學專科醫師、台灣國際醫療保健醫學專科醫師

減重藥物之新進展

Lin,Wen-Yuan MD, MS, PhD
China Medical University
China Medical University Hospital

Ideal Anti-obesity Drug

- Lower BW more than a low-calorie diet
- 10~20% weight loss for long term(2 years)
- Most of the weight loss(>75%) from fat
- BP, glucose, insulin, TCHOL, TG, LDL-C should be lowered proportionally to the amount of weight loss. HDL-C should increase
- Should not induce counter-regulatory mechanisms that may limits its efficacy
- Should be combined with other drugs, diet, and physical activity
- Well tolerated, no long-term toxicity
- Once-daily oral administration

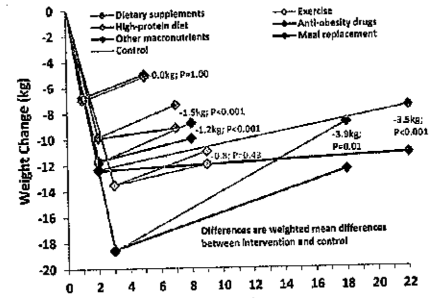
Table 1. Key Features of the Food and Drug Administration's 2007 Draft Obesity Drug Guidance

Target population
BMI ≥27 kg/m² plus a weight-related comorbidity or a BMI ≥30 kg/m²
Size and duration of the phase 3 clinical trials
≥4500 Overweight and obese subjects studied for at least 1 y
Efficacy criteria
Mean placebo-subtracted weight loss ≥5% or proportion of drug-treated subjects who lose ≥5% of baseline body weight is ≥35% and approximately double the proportion who lose ≥5% in the placebo group
Secondary end points of interest
Blood pressure and pulse
Lipoprotein lipids
Fasting glucose and insulin
Hemoglobin A_{1c} (in diabetics)
Waist circumference
Quality of life
Primary analysis population
Intention to treat

BMI indicates body mass index.

Circulation. 2012;125:2156-2164

Overview of changes in body weight during the rapid weight loss phase and the weight-loss maintenance period in 20 randomized controlled trials



Am J Clin Nutr doi: 10.3945/ajcn.113.070052.

3 major groups of drugs used to manage obesity

- Centrally acting medications that impair dietary intake
- Medications that act peripherally to impair dietary absorption
- Medications that increase energy expenditure

Anti-obesity medications withdrawn (Suspension of licensing for antiobesity drugs)

Drug	Year	Reason for suspension
Dinitrophenol	1938	Dermatitis, neuropathy, agranulocytosis, visual impairment, death
Aminorex	1968	Chronic pulmonary hypertension
Amphetamines (schedule II)	1971	Addiction, hypertension, myocardial toxicity
Fenfluramine/dexfenfluramine alone or in combination with phentermine	1997	Valvular heart disease
Phenylpropanolamine	2000	Hemorrhagic stroke
Rimonabant	2009	Psychiatric disorders, depression, suicidal ideation
Sibutramine	2010	Risk of major cardiovascular events

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Drugs With US Food and Drug Administration–Approved Indication for Obesity

Drug	Reference	N (T2D)	BMI (mean)	Age (mean)	1-year Δ%WL (mean)	% With >5% WL (versus placebo)	Frequent side effects	Uncommon side effects
Lorcaserin	[Smith et al. 2010] (BLOOM)	3182 (0)	36.2	44.1	3.7%	45% versus 20%	Dry mouth, Fatigue, Dizziness, Headache	Nausea, Urinary tract infection, Constipation/diarrhoea, Hypoglycaemia (in patients with T2D)
Lorcaserin	[Fidler et al. 2011] (BLOSSOM)	4008 (0)	35.9	43.8	3.0%	47% versus 25%		
Lorcaserin	[O'Neil et al. 2012] (BLOOM-DM)	604 (604)	36.0	52.4	3.5%	45% versus 16%		
Phentermine/topiramate	[Allison et al. 2012] (EQUIP)	1267 (0)	42.2	42.6	9.4%	67% versus 17%	Paraesthesia, Dry mouth, Constipation, Headache, Dysgeusia, Insomnia, Dizziness	Palpitations, Disturbances in attention, Alopecia, Diarrhoea, Anxiety and irritability, Depression/fatigue, Blurred vision, Glaucoma
Phentermine/topiramate	[Gadde et al. 2011] (CONQUER)	2487 (393)	36.6	51.1	8.6%	70% versus 21%		
Liraglutide	[Astrup et al. 2012]	398 (21)	34.8	45.9	4.9%	73% v 28%	Nausea, Vomiting	Pancreatitis
Liraglutide*	[Wadden et al. 2013]	422 (0)	35.6	46.2	6.1%	51% versus 21%	Constipation, Diarrhoea, Headache	

*Patients in this study were randomized after a run-in on a low calorie diet during which mean weight loss was 6%.
BMI, body mass index; T2D, type 2 diabetes mellitus; WL, weight loss.

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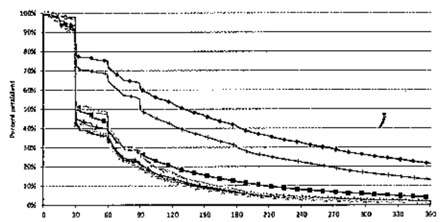
Table 1. Nationally Projected Characteristics of Antiobesity Drug Users in the United States, 2008–2011

	Benzphetamine	Diethylpropion	Orlistat	Phendimetrazine	Phentermine	Sibutramine	All Antiobesity Drugs
No. of users[a]	69,625	299,374	133,030	783,614	6,232,462	233,060	7,276,261
2008	22,991	102,641	68,979	253,503	1,883,164	117,125	2,348,838
2009	27,003	105,841	48,133	250,290	2,301,056	99,579	2,727,723
2010	25,503	99,952	34,030	251,043	2,431,963	63,697	2,798,618
2011	22,017	85,542	23,134	253,240	2,434,061	106	2,738,084
Female[a]	79.9%	86.3%	78.6%	87.0%	85.2%	82.3%	85.0%
Age (yrs)							
0–16	0.3%	0.5%	0.6%	0.5%	0.5%	0.6%	0.5%
17–44	52.6%	49.7%	39.9%	58.7%	64.1%	48.3%	62.3%
45–64	43.7%	44.6%	49.0%	38.7%	34.3%	46.1%	35.7%
≥ 65	5.3%	7.3%	12.2%	4.1%	3.1%	6.2%	3.6%
No. of dispensings[b]	358,017	1,049,442	484,005	3,191,475	25,335,191	720,419	31,138,551
Payer type[c]							
Cash	71.1%	66.2%	22.8%	70.9%	57.5%	41.3%	58.4%
Third party	28.9%	33.7%	68.5%	29.9%	42.3%	57.9%	41.3%
Medicaid	0.0%	0.1%	8.7%	0.1%	0.1%	0.8%	0.3%
BMI (kg/m²)[c]							
≤ 24.9	–[d]	4.4%	2.6%	7.0%	4.6%	1.3%	4.5%
25–26.9	–	7.5%	1.0%	6.3%	6.6%	1.0%	6.0%
27–29.9	–	10.6%	9.0%	8.1%	14.1%	9.2%	12.7%
≥ 30	–	62.8%	71.9%	74.6%	63.3%	73.3%	65.7%
Not specified	–	14.2%	15.3%	3.9%	11.3%	14.9%	11.1%

(Pharmacotherapy 2013)

Persistence by duration of use, longest episode/patient.
(Data source: Source Healthcare Analytics Source Lx, 2002–2011.)



(Pharmacotherapy 2013)

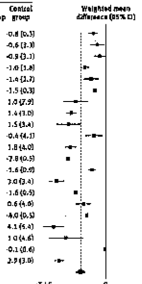
Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials

- Subjects: overweight or obese patients with or without type 2 diabetes mellitus.
- Received exenatide twice daily, exenatide once weekly, or liraglutide once daily at clinically relevant doses for at least 20 weeks.

BMJ 2012;344:d7771 doi: 10.1136/bmj.d7771

GLP-1 receptor agonist: change in body weight (kg)

BMJ 2012;344:d7771 doi: 10.1136/bmj.d7771



Trial	No of patients: GLP-1R agonist group	No of patients: Control group	Mean change (standard deviation): GLP-1R agonist group	Mean change (standard deviation): Control group	Weight (%)	Weighted mean difference (95% CI)
Bergenstal 2010	160	166	-2.3 (3.0)	-0.8 (0.3)	4.98	-1.50 (-1.97 to -1.03)
Buse 2004	129	123	-1.6 (3.4)	-0.6 (3.3)	4.74	-1.00 (-1.83 to -0.17)
Kendall 2005	241	247	-1.6 (3.1)	-0.9 (3.1)	4.93	-0.70 (-1.26 to -0.14)
Pratley 2010	221	219	-3.4 (3.0)	-1.0 (1.8)	4.98	-2.42 (-2.88 to -1.96)
Moretto 2008	78	78	-3.1 (2.7)	-1.4 (2.7)	4.76	-1.70 (-2.53 to -0.87)
Nauck 2009	242	122	-2.8 (0.2)	-1.5 (0.3)	5.09	-1.30 (-1.36 to -1.24)
Garber 2009	246	248	-2.5 (7.8)	1.0 (7.9)	4.21	-3.50 (-4.89 to -2.11)
Diamant 2010	233	223	-2.6 (3.1)	1.4 (3.0)	4.93	-4.00 (-4.55 to -3.45)
DeFronzo 2010	45	45	-2.8 (3.4)	1.5 (3.4)	4.21	-4.30 (-5.69 to -2.91)
Russell-Jones 2009	230	114	-1.8 (5.0)	-0.4 (4.1)	4.59	-1.39 (-2.38 to -0.38)
Heine 2005	282	267	-2.3 (3.9)	1.8 (4.0)	4.86	-4.10 (-4.76 to -3.44)
Astrup 2009	93	98	-7.2 (0.5)	-2.8 (0.5)	5.08	-4.40 (-4.54 to -4.26)
Elkin 2010	30	30	-3.2 (0.5)	-1.6 (0.9)	4.99	-1.60 (-2.04 to -1.16)
Davies 2009	118	117	-2.7 (3.4)	3.0 (3.4)	4.72	-5.71 (-6.57 to -4.85)
Rosenstock 2010	73	70	-5.1 (0.5)	-1.6 (0.5)	5.09	-3.50 (-3.66 to -3.34)
Zinman 2009	178	177	-2.0 (4.0)	0.6 (4.0)	4.74	-2.60 (-3.43 to -1.77)
Apovian 2010	96	98	-6.2 (0.5)	-4.0 (0.5)	5.08	-2.19 (-2.34 to -2.04)
Bergenstal 2009	124	124	-1.9 (3.8)	4.1 (5.4)	4.44	-6.00 (-7.16 to -4.84)
Bunck 2009	36	33	-3.6 (3.6)	1.0 (4.6)	3.59	-4.60 (-6.56 to -2.66)
Marre 2009	234	114	-0.2 (0.0)	-0.1 (0.6)	5.09	-0.10 (-0.72 to 0.07)
Nauck 2007	253	248	-2.5 (3.2)	2.9 (3.0)	4.94	-5.40 (-5.94 to -4.86)
Overall: P=0.00					100.00	-2.90 (-3.59 to -2.22)

Saxenda® for the treatment of obesity receives positive 14-1 vote in favour of approval from FDA Advisory Committee 11 September 2014

Novo Nordisk today announced that the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the United States Food and Drug Administration (FDA) has completed its meeting regarding the New Drug Application (NDA) for Saxenda®, the intended brand name for liraglutide 3 mg, a once- daily human GLP-1 analogue for the treatment of obesity.
The panel members voted 14-1 that the overall benefit-risk assessment Saxenda® was favourable and supports approval for chronic weight management in individuals with a BMI 30 kg/m2 or greater, or 27 kg/m2 or greater in the presence of at least one weight-related comorbidity.

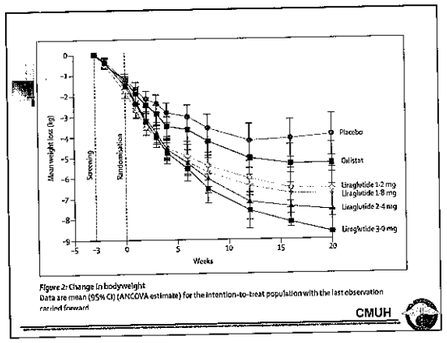


Figure 2: Change in bodyweight
Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward

CMUH

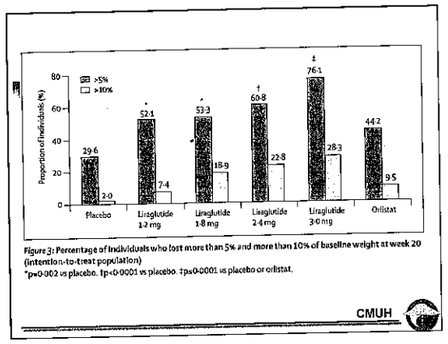
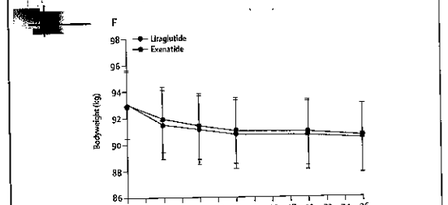


Figure 3: Percentage of individuals who lost more than 5% and more than 10% of baseline weight at week 20 (intention-to-treat population)
*p=0·002 vs placebo. †p<0·0001 vs placebo. ‡ps0·0001 vs placebo or orlistat.

CMUH

Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)

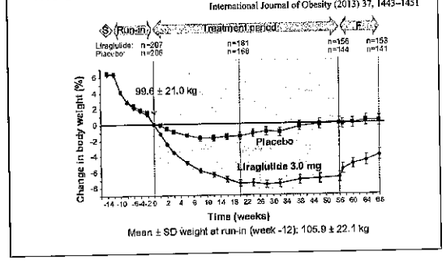
Lancet 2009; 374: 39–47



CMUH

Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study

International Journal of Obesity (2013) 37, 1443–1451



Mean ± SD weight at run-in (week -12): 105.9 ± 22.1 kg

Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study

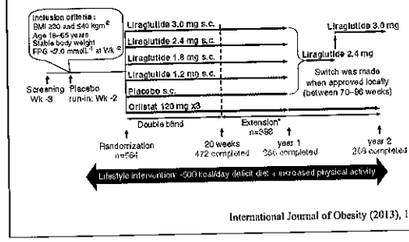
International Journal of Obesity (2013) 37, 1443–1451

Table 3 Changes in body weight measures from randomization

	Change from randomization to week 56		ETD or OR for liraglutide versus placebo (95% CI), P-value
	Liraglutide 3.0 mg (n 207)	Placebo (n 206)	
Co-primary end points			
Body weight (% change)	6.2 (7.3)	0.2 (7.6)	ETD 6.1 (5.5 to 6.6), P<0.0001
Proportion maintaining ≥5% run-in weight loss	81.6%	48.8%	OR 4.8 (3.0 to 7.7), P<0.0001
Proportion with ≥5% weight loss	50.5%	21.8%	OR 3.9 (2.4 to 6.1), P<0.0001
Secondary end points			
Body weight (kg)	6.0 (7.3)	0.1 (7.6)	ETD 5.9 (5.3 to 6.4), P<0.0001
Proportion with ≥10% weight loss	26.1%	6.3%	OR 5.3 (2.9 to 10.1), P<0.0001
BMI (kg/m²)	2.1 (2.6)	0.0 (2.7)	ETD 2.1 (1.9 to 2.3), P<0.0001
Waist circumference (cm)	4.7 (7.4)	1.3 (6.4)	ETD 3.5 (3.0 to 3.9), P<0.0001
	Change from randomization to week 68 (follow-up) for participants entering follow-up		ETD for liraglutide versus placebo (95% CI), P-value
	(n 159)	(n 144)	
Body weight (% change)	4.1 (8.2)	0.3 (7.7)	4.2 (3.0 to 5.4), P<0.0001

Abbreviations: BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference; OR, odds ratio. Changes from randomization to week 56 or week 68 are observed means (±SD). ETDs are from an analysis of covariance and ORs are from a logistic regression analysis, all using the full analysis set and with the last observation carried forward, except for participant weight loss data at week 68, which was without last observation carried forward. Body weight was measured in the fasting state.

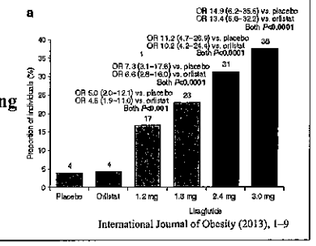
Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults



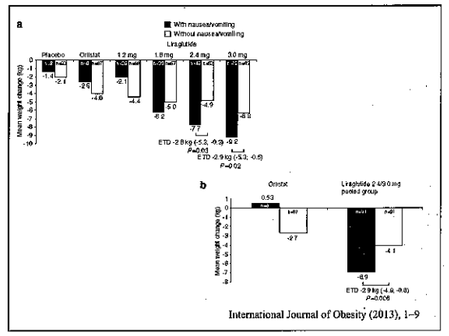
International Journal of Obesity (2013), 1–9

Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults

The proportion of individuals reporting **nausea/vomiting** at any time during year 1



International Journal of Obesity (2013), 1–9



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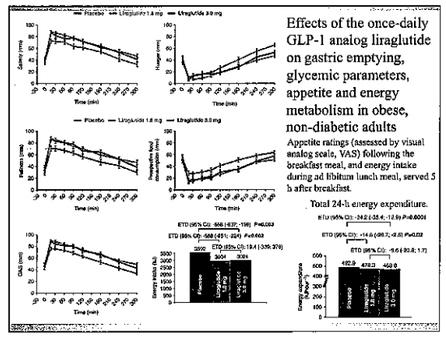


Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults

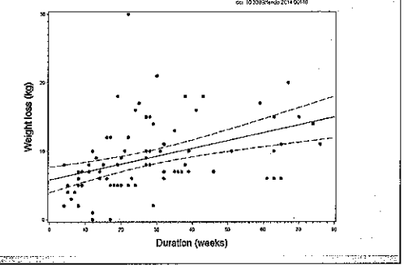
Appetite ratings (assessed by visual analog scale, VAS) following the breakfast meal, and energy intake during ad libitum lunch meal, served 5 h after breakfast.

Total 24-h energy expenditure.

The effect of liraglutide on weight loss in women with polycystic ovary syndrome: an observational study

Christina B. Rasmussen* and Svend Lindenberg

CLINICAL CASE STUDY



Benefits of Liraglutide Treatment in Overweight and Obese Older Individuals With Prediabetes

Diabetes Care 36:3276–3282, 2013

Liraglutide in prediabetes

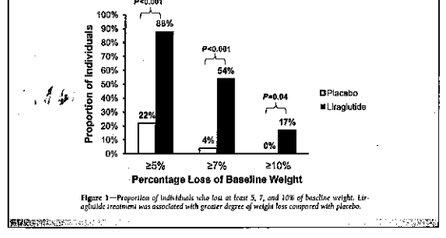
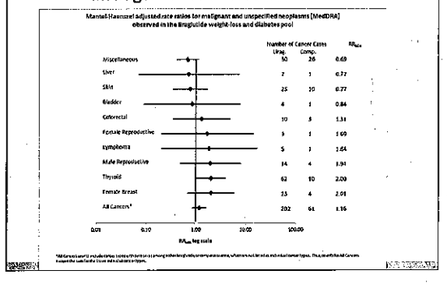
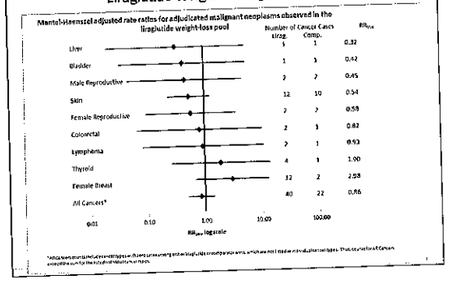


Figure 1—Proportion of individuals who lost at least 5, 7, and 10% of baseline weight. Liraglutide treatment was associated with greater degree of weight loss compared with placebo.

Mantel-Haenszel-Adjusted Rate Ratios for Adjudicated Malignant Neoplasms Observed in the Liraglutide Weight Management and Diabetes Pool Pool



Mantel-Haenszel-Adjusted Rate Ratios for Malignant and Unspecified Neoplasms (MedDRA) Observed in the Liraglutide Weight Management Pool



Approved anti-obesity drug in US

BELVIQ - QSYMIA

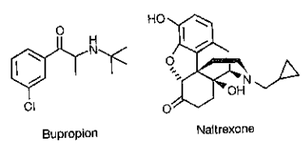
APPROVED

Contrave
(naltrexone HCl/bupropion HCl)
8 mg/90 mg • Extended-Release tablets

Contrave: Naltrexone/Bupropion Combo Pill

New Weight Loss Drug Advances

Chemical Composition of Contrave



FDA News Release:
FDA approves weight-management drug Contrave on September 10, 2014

----------INDICATIONS AND USAGE----------

CONTRAVE is a combination of naltrexone, an opioid antagonist, and bupropion, an aminoketone antidepressant, indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia). (1)

Limitations of Use:

- The effect of CONTRAVE on cardiovascular morbidity and mortality has not been established. (1)
- The safety and effectiveness of CONTRAVE in combination with other products intended for weight loss, including prescription and over-the-counter drugs, and herbal preparations, have not been established. (1)

----------DOSAGE AND ADMINISTRATION----------

CONTRAVE dose escalation schedule (2.1):

	Morning Dose	Evening Dose
Week 1	1 tablet	None
Week 2	1 tablet	1 tablet
Week 3	2 tablets	1 tablet
Week 4 – Onward	2 tablets	2 tablets

----------DOSAGE FORMS AND STRENGTHS----------

Extended-Release Tablets: 8 mg naltrexone HCl /90 mg bupropion HCl (3)

----------CONTRAINDICATIONS----------

- Uncontrolled hypertension (4)
- Seizure disorders, anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs (4)
- Use of other bupropion-containing products (4)
- Chronic opioid use (4)
- During or within 14 days of taking monoamine oxidase inhibitors (MAOI) (4)
- Known allergy to any of the ingredients in CONTRAVE (4)
- Pregnancy (4)

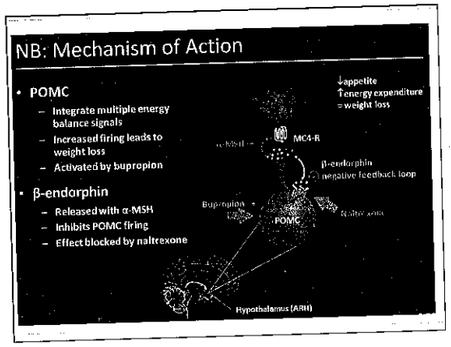
WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

See full prescribing information for complete boxed warning

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder and other psychiatric disorders. (5.1)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.1)**
- **Serious neuropsychiatric events have been reported in patients taking bupropion for smoking cessation. (5.2)**
- **CONTRAVE has not been studied in pediatric patients. (5.1)**

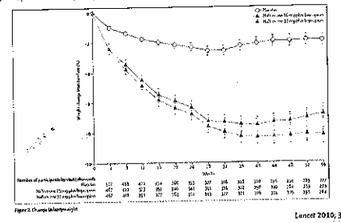
NB: Mechanism of Action

- **POMC**
  - Integrate multiple energy balance signals
  - Increased firing leads to weight loss
  - Activated by bupropion
- **β-endorphin**
  - Released with α-MSH
  - Inhibits POMC firing
  - Effect blocked by naltrexone



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, Ken Fujioka, Wayne A Plodkowski, Stanley Mudaliar, Maria Guttadauria, Janelle Erickson, Dennis D Kim, Eduardo Dunayevich, for the COR-I Study Group*

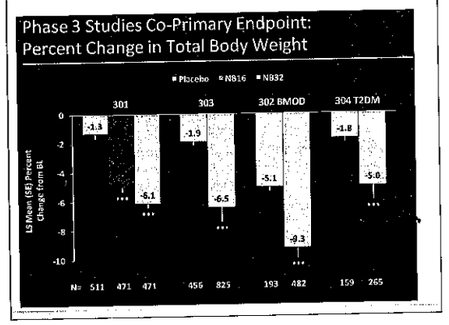


Lancet 2010; 376: 595–605

	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	39 (6·9%)	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%)	41 (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	19 (3·1%)	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%)

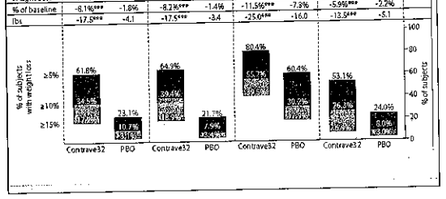
Lancet 2010; 376: 595–605

Phase 3 Studies Co-Primary Endpoint: Percent Change in Total Body Weight



Contrave Obesity Research (COR) Program
Contrave (naltrexone sustained release (SR)/bupropion SR)

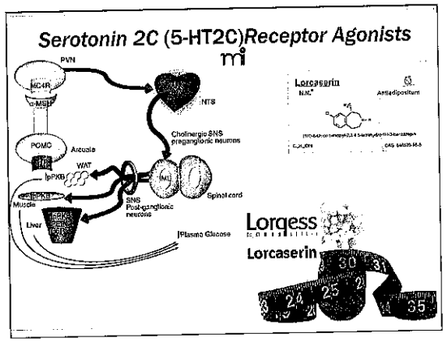
Weight Loss	COR-I Contrave32 N=296	COR-I PBO N=290	COR-II Contrave32 N=434	COR-II PBO N=287	COR-BMOD Contrave32 N=301	COR-BMOD PBO N=106	COR-Diabetes Contrave32 N=175	COR-Diabetes PBO N=109
% of baseline	-8.1%***	-1.8%	-8.2%***	-1.4%	-11.5%***	-7.9%	-5.9%***	-2.2%
lbs	-17.5***	-4.1	-17.5***	-3.4	-25.6***	-16.0	-13.5***	-5.1



Contrave Obesity Research (COR) Program
Contrave (naltrexone sustained release (SR)/bupropion SR)

	COR-I Contrave32	COR-I PBO	COR-II Contrave32	COR-II PBO
Waist circumference, cm	-6.2***	-2.5	-6.7***	-2.1
Triglycerides, %	-12.7***	-3.1	-9.8***	-0.5
Fasting HDL, %	8.0***	0.8	8.2***	-0.8
Fasting LDL, %	-2.0	-0.5	-3.6**	0.3
hsCRP, %[1]	-29.0**	-16.7	-28.8***	-8.3
HOMA-IR, %[2]	-20.2***	-5.9	-13.8***	1.2
	COR-BMOD Contrave32	**COR-BMOD PBO**	**COR-Diabetes Contrave32**	**COR-Diabetes PBO**
Waist circumference, cm	-10.0***	-6.8	-5.0**	-2.9
Triglycerides, %	-16.6**	-8.5	-11.2**	-0.8
Fasting HDL, %	9.4***	2.8	7.4***	-0.2
Fasting LDL, %	7.1	10.0	2.4	4.2
hsCRP, %[1]	-25.9	-16.9	-20.9	-13.3
HOMA-IR, %[2]	-29.9**	-16.6	-20.6	-14.7

Serotonin 2C (5-HT2C)Receptor Agonists



Lorcaserin hydrochloride ("lorcaserin")

- Lorcaserin is a selective serotonin 2C (5-HT2C) receptor agonist that reduces body weight by reducing food intake.
- 5-HT2B- fenfluramine-Serotonin valvulopathy
- 5-HT2A-mood and perceptual effects
- Lorcaserin selectivity for the 5-HT2C receptor is approximately 15-fold and 100-fold relative to the 5-HT2A and 5-HT2B receptors
- Lorcaserin is only a partial 5-HT2A agonist

INDICATIONS AND USAGE

BELVIQ is a serotonin 2C receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) (1) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition, (e.g., hypertension, dyslipidemia, type 2 diabetes) (1)

Limitations of Use:

- The safety and efficacy of coadministration with other products for weight loss have not been established (1)
- The effect of BELVIQ on cardiovascular morbidity and mortality has not been established (1)

DOSAGE AND ADMINISTRATION

- One tablet of 10 mg twice daily (2)
- Discontinue if 5% weight loss is not achieved by week 12 (2)

DOSAGE FORMS AND STRENGTHS

10 mg film-coated tablets (3)

CONTRAINDICATIONS

Pregnancy (4)

	研究一	研究二	研究三 BLOSSOM trial	研究四 BLOOM-DM trial
Published	Obesity(2008)	NEJM(2010)	JCEM(2011)	Obesity(2012)
受試人數	469	3182	4008	604
BMI (kg/m^2)	30-45	30-45 或 27-45 kg/m^2、同時已有高血壓、高脂血症、心血管病	30-45 或 27-29.9 kg/m^2、同時已有高血壓、高脂血症、心血管病	27-45
排除糖尿病	有	有	有	無
Dose-related effect	有	有	有	無
重大副作用	無	無	無	無

Lorcaserin (APD356), a Selective 5-HT$_{2C}$ Agonist, Reduces Body Weight in Obese Men and Women
Obesity (2008) 17, 494–503.

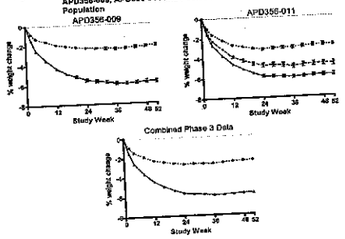
Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management
N Engl J Med 2010;363:245-56.

A One-Year Randomized Trial of Lorcaserin for Weight Loss in Obese and Overweight Adults: The BLOSSOM Trial
J Clin Endocrinol Metab 96: 3067–3077, 2011

Randomized Placebo-Controlled Clinical Trial of Lorcaserin for Weight Loss in Type 2 Diabetes Mellitus: The BLOOM-DM Study
Obesity (2012) 20, 1426–1436

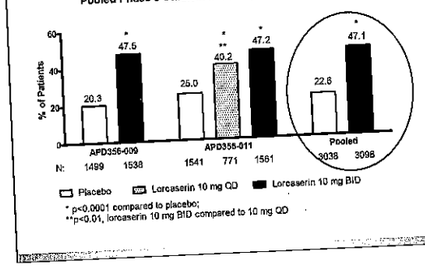
Phase 3 study

Figure 14. Mean Weight Change (%) from Baseline to Week 52 in APD356-009, APD356-011 and Pooled Phase 3 Studies: MITT Population



Phase 3 study

Figure 13. Proportion of Patients Achieving ≥5% Reduction in Body Weight after 52 Weeks of Treatment in APD356-009, APD356-011 and Pooled Phase 3 Studies: MITT Population

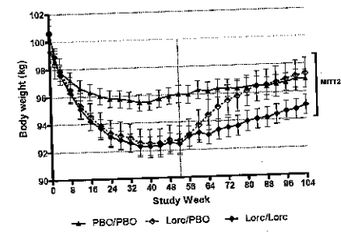


Phase 3 study

Table 17. Proportion of Patients Achieving ≥5% Reduction in Body Weight after 52 Weeks in Phase 3 Studies: MITT Population

Treatment	N	n (%)	Difference in Proportion (%) (95% CI)[a]	Odds Ratio (95% CI)[b]	p-Value[b]
APD356-009					
Placebo	1499	304 (20.3)			
Lorcaserin 10 mg BID	1538	731 (47.5)	27.2 (24.0, 30.5)	3.56 (3.03, 4.18)	<0.001
Between treatment comparison: Lorcaserin 10 mg BID vs. Placebo					
APD356-011					
Placebo	1541	385 (25.0)			
Lorcaserin 10 mg BID	1561	737 (47.2)	22.23 (18.94, 25.52)	2.69 (2.31, 3.13)	<0.001
Between treatment comparison: Lorcaserin 10 mg BID vs. Placebo					
POOLED PHASE 3 DATA					
Pooled Placebo	3038	687 (22.61)			
Pooled Lorcaserin 10 mg BID	3098	1460 (47.13)	24.52 (22.22, 26.82)	3.07 (2.75, 3.43)	<0.001
Between treatment comparison: Lorcaserin 10 mg BID vs. Placebo					

Figure 16. Change in Body Weight from Baseline to Week 104 in APD356-009: MITT2 Population



	Duration (years)	Sample size	Dropouts	Weight loss with drug	Weight loss with placebo
Orlistat					
Meta-analysis* of 13 randomised controlled trials	1–4	6196	~30%	-2.9kg*	NA
Lorcaserin					
BLOOM†	1	3182	50%	-5.8%	-2.2
BLOSSOM‡	1	3306	45%	-5.8%	-2.8
Naltrexone plus bupropion					
NB-301*	1	1164	50%	-5.1	-1.3
NB-302§*	1	793	42%	-9.3	-5.1
NB-303¶*	1	1496	46%	-6.5	-1.9
NB-304‖*	1	505	45%	-5.0	-1.8

In most cases, results were based on a modified intention-to-treat analysis of data for patients who took one dose of the study drug and had at least one follow-up assessment. In some studies, overweight patients were included in addition to those who were obese. There were many differences between studies in terms of the eligibility criteria. For lorcaserin and naltrexone plus bupropion, data are shown for the most effective dose when more than one dose was tested. NA=not applicable. *Relative to placebo. †First-year data only. ‡Data are for the highest dose (10 mg twice a day). §Ancillary intensive lifestyle intervention was administered to all patients. ¶Patients showing inadequate response were rerandomised at 6 months to a higher dose. ‖Overweight or obese patients with diabetes.

Table 5: Current and emerging antiobesity drugs

Relative Risk of Adverse Event Preferred Terms Reported by ≥1% of Patients in Any Treatment Group and with RR >1 for Lorcaserin 10 mg BID Group Compared to Placebo

Preferred Term	Relative Risk	Lower 95% Confidence Limit	Upper 95% Confidence Limit	% of Patients in Lorcaserin Group
Chills	5.32	2.23	12.69	1.0
Paraesthesia	2.48	1.35	4.57	1.2
Vision blurred	2.42	1.20	4.90	1.1
Dry mouth	2.28	1.74	2.98	5.3
Dizziness	2.21	1.79	2.72	9.8
Somnolence	2.03	1.26	3.27	1.8
Fatigue	2.00	1.61	2.48	7.2
Vulvovaginal mycotic infection	1.72	1.12	2.63	1.9
Menorrhagia	1.72	0.96	3.06	1.0
Vertigo	1.71	1.09	2.92	1.1
Alopecia	1.70	1.10	2.65	1.7
Tension headache	1.70	0.98	2.94	1.1
Headache	1.67	1.47	1.90	18.8
Abdominal pain upper	1.60	1.07	2.39	1.9
Respiratory tract congestion	1.60	0.91	2.78	1.0
Neck pain	1.57	0.99	2.50	1.3
Nausea	1.56	1.28	1.87	8.3
Musculoskeletal pain	1.51	1.03	2.21	2.0
Constipation	1.48	1.19	1.85	6.8
Seasonal allergy	1.48	0.95	2.30	1.5

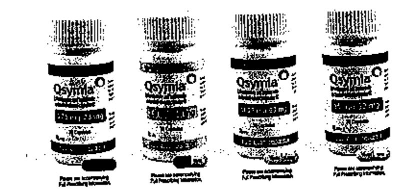
WORSENING OF PRE-EXISTING VALVULOPATHY WITH A NEW OBESITY DRUG LORCASERIN, A SELECTIVE 5-HYDROXYTRYPTAMINE 2C RECEPTOR AGONIST: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

1. Compared to placebo, increase in preexisting aortic regurgitation (AR) was significantly higher with lorcaserin 20mg daily (p=0.01) but not with 10mg daily (p=0.94) .
2. Increase in preexisting mitral regurgitation (MR) was not significantly different between lorcaserin and placebo, (p=0.15 in 20mg daily, p=0.4 in 10mg daily).
3. Development of new valvulopathy was not significantly different between lorcaserin and placebo (p=0.75 in 20mg daily, p=0.5 in 10mg daily)

Combination of the drugs *phentermine* and *topiramate* (trade name Qsymia)

QSYMIA
Another Tool For Success

Qsymia - 4 different dose



Indication

Qsymia is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m2 or greater (obese) or
- 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia

Limitations of Use:

- The effect of Qsymia on **cardiovascular morbidity and mortality** has not been established
- The safety and effectiveness of Qsymia in combination with other products intended for weight loss, including prescription and over-the-counter drugs, and herbal preparations, have not been established

Identify Appropriate Patients

- BMI 30 or greater (obese) or BMI 27 or greater (overweight) with at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia
- **Must NOT be pregnant**, trying to get pregnant, or unable/unwilling to comply with contraceptive guidance
- No glaucoma
- No hyperthyroidism
- Not using monoamine oxidase inhibitors (MAOIs) or have not used within 14 days
- No known hypersensitivity or idiosyncrasy to the sympathomimetic amines

- FDA has required a **Risk Evaluation and Mitigation Strategy (REMS)** for Qsymia so that healthcare providers can be informed about the increased risk of teratogenicity associated with Qsymia therapy

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

Obesity (2011) 20, 330–342

David B. Allison[1,2], Kishore M. Gadde[3], William Timothy Garvey[2,4], Craig A. Peterson[5], Michael L. Schwiers[6], Thomas Najarian[5], Peter Y. Tam[5], Barbara Troupin[5] and Wesley W. Day[5]

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

Lancet 2011; 377: 1341-52

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]

W Timothy Garvey, Donna H Ryan, Michelle Look, Kishore M Gadde, David B Allison, Craig A Peterson, Michael Schwiers, Wesley W Day, and Charles H Bowden

Am J Clin Nutr 2012;95:297–308

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

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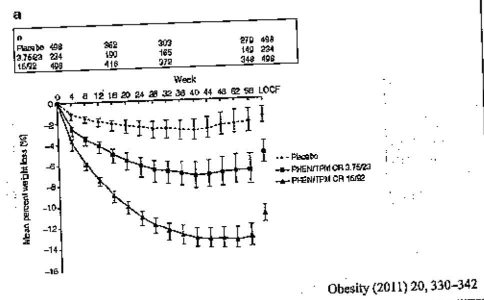
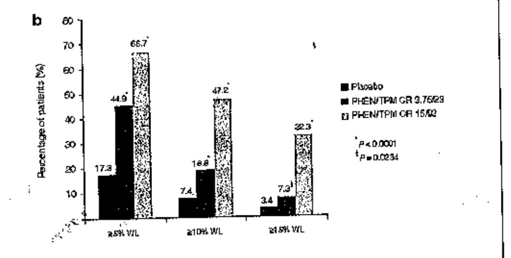
Obesity (2011) 20, 330–342

Mean percent weight loss



Obesity (2011) 20, 330–342

Patients achieving ≥5%, ≥10%, and ≥15% weight loss



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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

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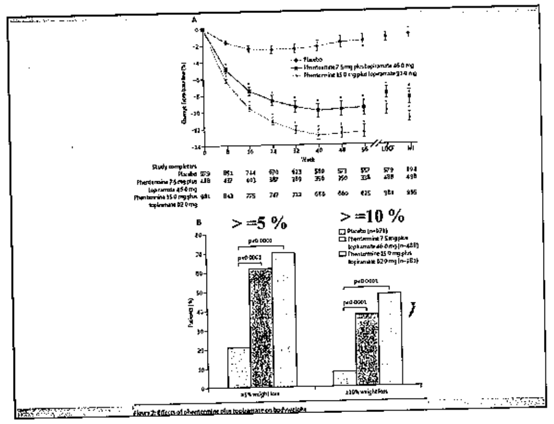


Figure 3: Effects of phentermine plus topiramate on cardiometabolic variables in high-risk patients

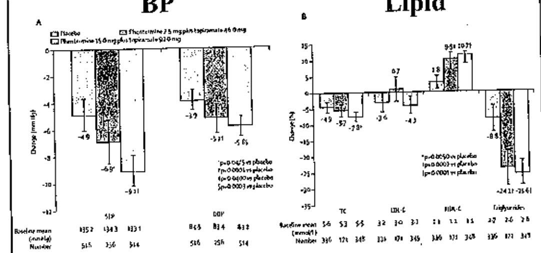
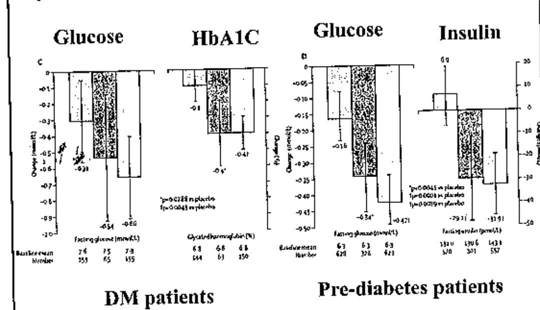
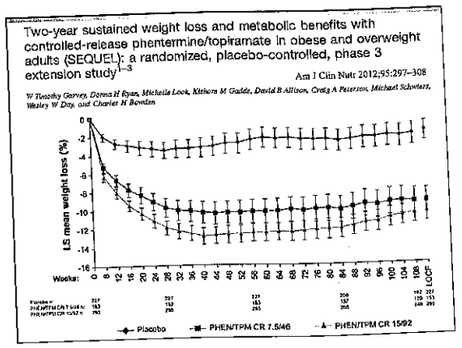


Figure 3: Effects of phentermine plus topiramate on cardiometabolic variables in high-risk patients



Adverse events in the safety population (n=2485)*

	Placebo (n=993)	Phentermine 7.5 mg plus topiramate 46.0 mg (n=498)	p value	Phentermine 15.0 mg plus topiramate 92.0 mg (n=994)	p value
Dry mouth	24 (2%)	67 (13%)	<0.0001	207 (21%)	<0.0001
Paraesthesia	20 (2%)	68 (14%)	<0.0001	204 (21%)	<0.0001
Constipation	59 (6%)	75 (15%)	<0.0001	173 (17%)	<0.0001
Upper respiratory tract infection	128 (13%)	61 (12%)	0.7471	133 (13%)	0.7906
Nasopharyngitis	86 (9%)	53 (11%)	0.3204	98 (10%)	0.3947
Dysgeusia	11 (1%)	37 (7%)	<0.0001	103 (10%)	<0.0001
Insomnia	47 (5%)	29 (6%)	0.3872	102 (10%)	<0.0001
Headache	90 (9%)	35 (7%)	0.1583	101 (10%)	0.4467
Dizziness	31 (3%)	36 (7%)	0.0005	99 (10%)	<0.0001
Sinusitis	67 (7%)	34 (7%)	1.0000	85 (9%)	0.1511
Back pain	49 (5%)	28 (6%)	0.6199	71 (7%)	0.0386
Nausea	42 (4%)	18 (4%)	0.6754	68 (7%)	0.0139
Fatigue	50 (5%)	22 (4%)	0.7010	67 (7%)	0.1270
Diarrhoea	48 (5%)	32 (6%)	0.2229	58 (6%)	0.3690
Blurred vision	36 (4%)	20 (4%)	0.7729	60 (6%)	0.0157
Urinary tract infection	37 (4%)	26 (5%)	0.3753	54 (5%)	0.0855
Arthralgia	54 (5%)	23 (5%)	0.5373	44 (4%)	0.3035
Bronchitis	43 (4%)	22 (4%)	1.0000	52 (5%)	0.4004
Psychiatric adverse events†					
Depression	29 (3%)	14 (3%)	0.9054	39 (4%)	0.3188
Anxiety	21 (2%)	9 (2%)	0.6899	41 (4%)	0.0100
Irritability‡	8 (<1%)	13 (3%)	0.0053	34 (3%)	<0.0001
Time to onset (days; median, IQR)	52 (26–164)	36 (8–138)	0.6988	29 (17–118)	0.0049
Duration (days; median, IQR)	44 (17–121)	35 (11–83)	0.3989	29 (12–63)	0.0251
Resolution among patients discontinuing drug	4/5 (80%)	10/10 (100%)	0.3333	33/37 (89%)	0.4876
Cognitive adverse events§					
Disturbance in attention	7 (<1%)	10 (2%)	0.0360	35 (4%)	<0.0001
Time to onset (days; median, IQR)	22 (8–119)	33 (10–109)	0.8958	15 (11–58)	0.8123
Duration (days; median, IQR)	19 (13–76)	54 (8–149)	0.6457	16 (13–81)	0.7353
Resolution among subjects discontinuing drug	3/3 (100%)	2/2 (100%)	NA	11/11 (100%)	NA


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]

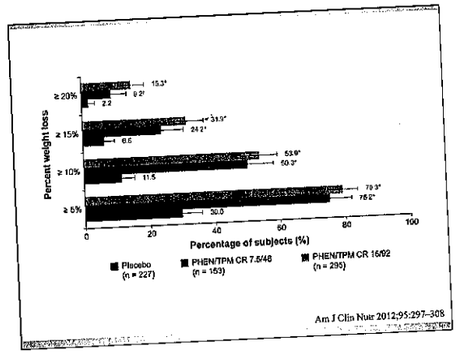
Am J Clin Nutr 2012;95:297–308

W Timothy Garvey, Donna H Ryan, Michelle Look, Kithsiri M Gadde, David B Allison, Craig A Peterson, Michael Schwiers, Wesley W Day, and Charles H Bowden

LS mean weight loss (%)

Weeks

Placebo — PHEN/TPM CR 7.5/46 — PHEN/TPM CR 15/92


Percent weight loss

≥ 20%

≥ 15%

≥ 10%

≥ 5%

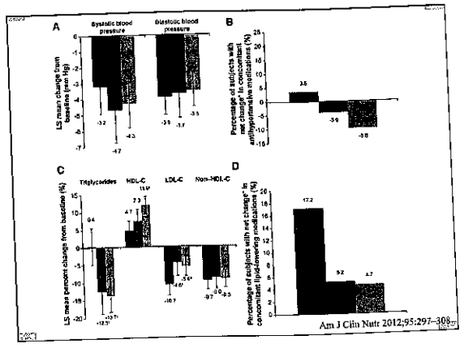
Percentage of subjects (%)

Placebo (n = 227)

PHEN/TPM CR 7.5/46 (n = 153)

PHEN/TPM CR 15/92 (n = 295)

Am J Clin Nutr 2012;95:297–308


A

Systolic blood pressure

Diastolic blood pressure

LS mean change from baseline (mm Hg)

B

Percentage of subjects with medical conditions with antihypertensive medications (%)

C

Triglycerides

HDL-C

LDL-C

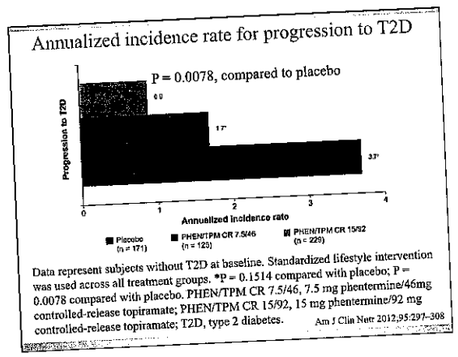
Non-HDL-C

LS mean percent change from baseline (%)

D

Percentage of subjects with net change in concomitant hypertensive medications (%)

Am J Clin Nutr 2012;95:297–308


Annualized incidence rate for progression to T2D

P = 0.0078, compared to placebo

Progression to T2D

Annualized incidence rate

Placebo (n = 171)

PHEN/TPM CR 7.5/46 (n = 123)

PHEN/TPM CR 15/92 (n = 229)

Data represent subjects without T2D at baseline. Standardized lifestyle intervention was used across all treatment groups. *P = 0.1514 compared with placebo; P = 0.0078 compared with placebo. PHEN/TPM CR 7.5/46, 7.5 mg phentermine/46mg controlled-release topiramate; PHEN/TPM CR 15/92, 15 mg phentermine/92 mg controlled-release topiramate; T2D, type 2 diabetes.

Am J Clin Nutr 2012;95:297–308

洪皓彰

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著作：

1. Ou HY, Wu HT, Lu FH, Su YC, Hung HC, Wu JS, Yang YC, Wu CL, Chang CJ. Activation of free fatty acid receptor 1 improves hepatic steatosis through a p38-dependent pathway. J Mol Endocrinol. 2014 Oct;53(2):165-74.
2. Wu HT, Lu FH, Su YC, Ou HY, Hung HC, Wu JS, Yang YC, Chang CJ. In vivo and in vitro anti-tumor effects of fungal extracts. Molecules. 2014 Feb 21;19(2):2546-56.
3. Hung HC, Lu FH, Ou HY, Wu JS, Yang YC, Chang CJ. Menopause is associated with self-reported poor sleep quality in women without vasomotor symptoms. Menopause. 2014 Aug;21(8):834-9.
4. Hung HC, Lu FH, Ou HY, Wu HT, Wu JS, Yang YC, Chang CJ. Increased cardiotrophin-1 in subjects with impaired glucose tolerance and newly diagnosed diabetes. Int J Cardiol. 2013 Nov 5;169(3):e33-4.
5. Wu HT, Lu FH, Ou HY, Su YC, Hung HC, Wu JS, Yang YC, Wu CL, Chang CJ. The role of Hepassocin in the development of non-alcoholic fatty liver disease. J Hepatol. 2013 Nov;59(5):1065-72.
6. Hung HC, Yang YC, Ou HY, Wu JS, Lu FH, Chang CJ. The association between self-reported sleep quality and overweight in a Chinese population. Obesity (Silver Spring). 2013 Mar;21(3):486-92.
7. Hung HC, Yang YC, Ou HY, Wu JS, Lu FH, Chang CJ. The association between self-reported sleep quality and metabolic syndrome. PLoS One. 2013;8(1):e54304.
8. Ou HY, Wu HT, Hung HC, Yang YC, Wu JS, Chang CJ. Multiple mechanisms of GW-9508, a selective G protein-coupled receptor 40 agonist, in the regulation of glucose homeostasis and insulin sensitivity. Am J Physiol Endocrinol Metab. 2013 Mar 15;304(6):E668-76.