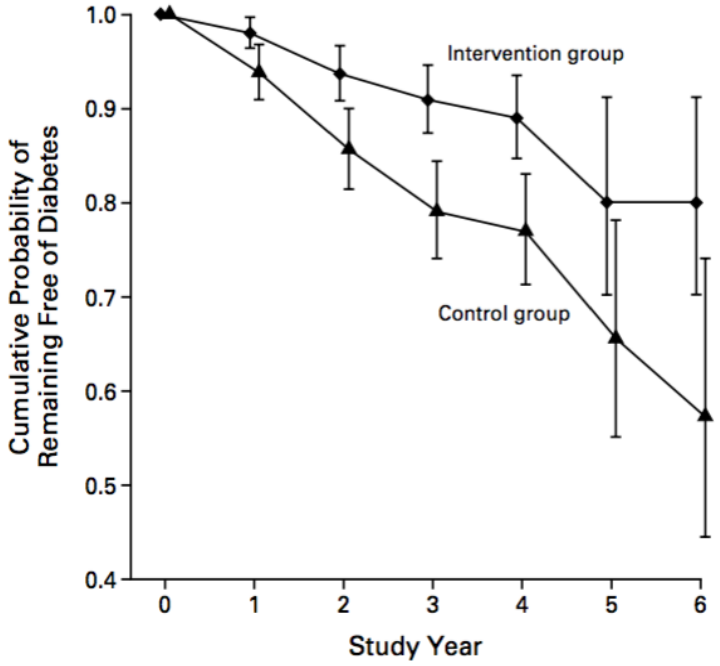
Pearl, 32

What did we and she do?

- Started on Metformin and Vildagliptin
  - (ideal medication would be a GLP1 agonist – slows gastric transit and helps with weight loss)
- Diet plan in the Gym (LCH) – encouraged to continue
- What happened?
  - Big smile
  - Hba1c 53mmol/mol
  - Weight down by 6kg
- Why did it work?

Time to review the evidence



Subjects at Risk						
Total no.	507	471	374	167	53	27
Cumulative no. with diabetes:						
Intervention group	5	15	22	24	27	27
Control group	16	37	51	53	57	59

Figure 1. Proportion of Subjects without Diabetes during the Trial.

The New England Journal of Medicine

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PREVENTION OF TYPE 2 DIABETES MELLITUS BY CHANGES IN LIFESTYLE AMONG SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE

JAAKKO TUOMILEHTO, M.D., PH.D., JAANA LINDSTRÖM, M.S., JOHAN G. ERIKSSON, M.D., PH.D., TIMO T. VALLE, M.D., HELENA HÄMÄLÄINEN, M.D., PH.D., PIRJO ILANNE-PARIKKA, M.D., SIRKKA KEINÄNEN-KIUKAANNIEMI, M.D., PH.D., MAURI LAAKSO, M.D., ANNE LOUHERANTA, M.S., MERJA RASTAS, M.S., VIRPI SALMINEN, M.S., AND MATTI UUSITUPA, M.D., PH.D., FOR THE FINNISH DIABETES PREVENTION STUDY GROUP

- During the trial, the risk of developing diabetes was **reduced by 58%** (P<0.001) in the intervention group.
- ***Conclusions:*** Type 2 diabetes can be prevented by changes in the lifestyles of high-risk subjects.

Time to review the evidence

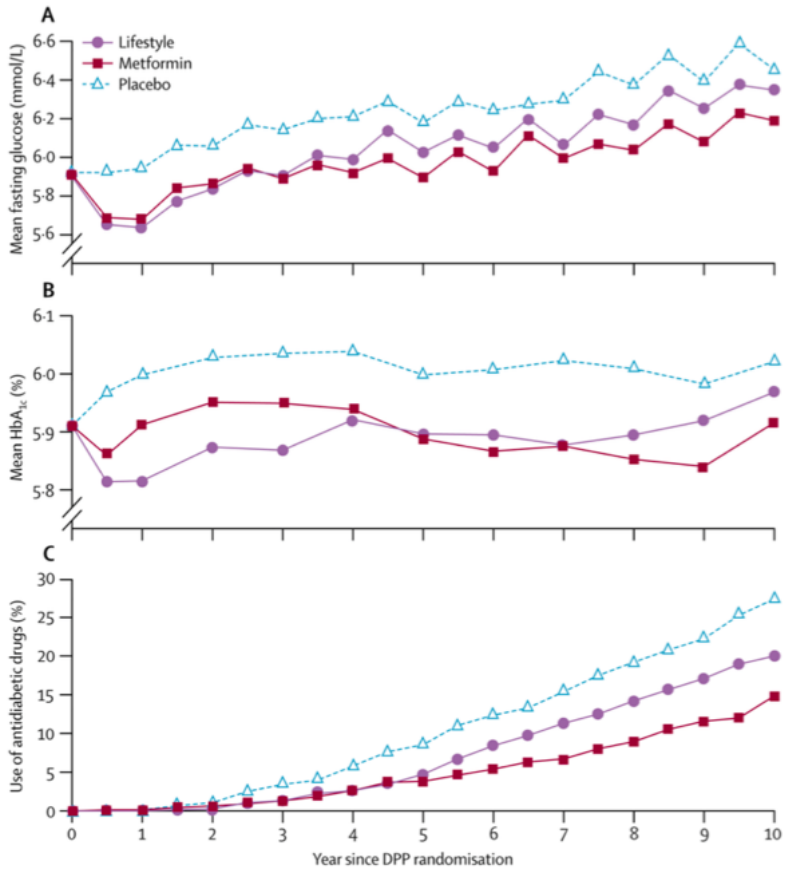

Figure 5. Fasting glucose, glycosylated haemoglobin, and antidiabetic drug use
A=fasting glucose in mmol/L. B=HbA_{1c} (%). C=use of antidiabetic drugs (%). All participants were included irrespective of whether they developed diabetes during follow-up. Study-assigned metformin is excluded from antidiabetic drug use. Information for each data point is shown in webappendix p 7.

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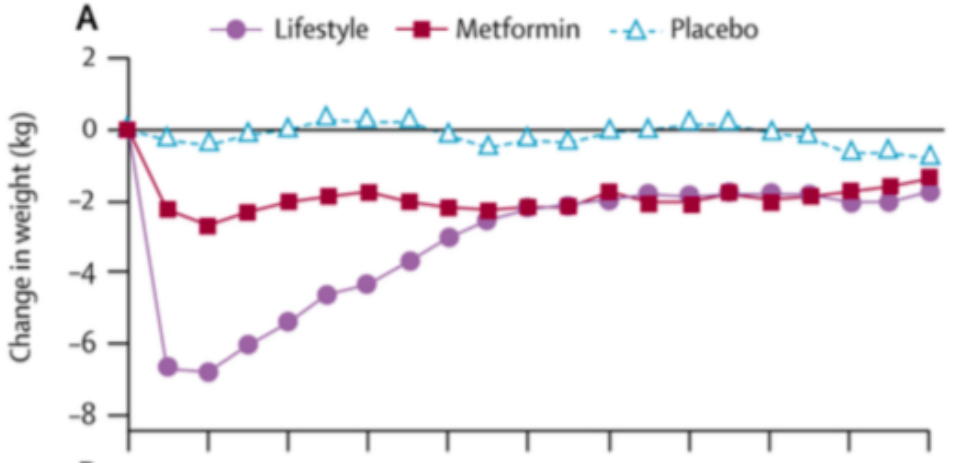
10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study

Diabetes Prevention Program Research Group*

Summary

Background—In the 2·8 years of the Diabetes Prevention Program (DPP) randomised clinical trial, diabetes incidence in high-risk adults was reduced by 58% with intensive lifestyle intervention and by 31% with metformin, compared with placebo. We investigated the persistence of these effects in the long term.



Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Michael EJ Lean, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Renae Stefanetti, Michael Trenell, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Naveed Sattar, Roy Taylor**

Summary

Background Type 2 diabetes is a chronic disorder that requires lifelong treatment. We aimed to assess whether intensive weight management within routine primary care would achieve remission of type 2 diabetes.

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http://dx.doi.org/10.1016/

	Intervention group (n=149)	Control group (n=149)
Sex		
Female	66 (44%)	56 (38%)
Male	83 (56%)	93 (62%)
White ethnicity	146 (98%)	147 (99%)
Age (years)	52·9 (7·6)	55·9 (7·3)
Weight (kg)	101·0 (16·7)	98·8 (16·1)
Body-mass index (kg/m²)	35·1 (4·5)	34·2 (4·3)
Waist (cm)	107·5 (8·4)	106·5 (8·9)
Systolic blood pressure (mm Hg)	132·7 (17·5)	137·2 (16·0)
Diastolic blood pressure (mm Hg)	84·6 (10·2)	85·5 (8·8)
Time since diabetes diagnosis (years)		
Mean (SD)	3·0 (1·7)	3·0 (1·8)
Median (range)	3·1 (0·0–6·0)	2·6 (0·2–6·0)
HbA_{1c}		
%	7·7 (1·25)	7·5 (1·05)
mmol/mol	60 (13·7)	58 (11·5)
Fasting glucose (mmol/L)	9·22 (3·29)	8·82 (2·54)
Prescribed oral antidiabetic medication	111 (74·5)	115 (77·2)
Number of oral antidiabetic medications		
0	38 (26%)	34 (23%)
1	65 (44%)	79 (53%)
≥2	46 (31%)	36 (24%)

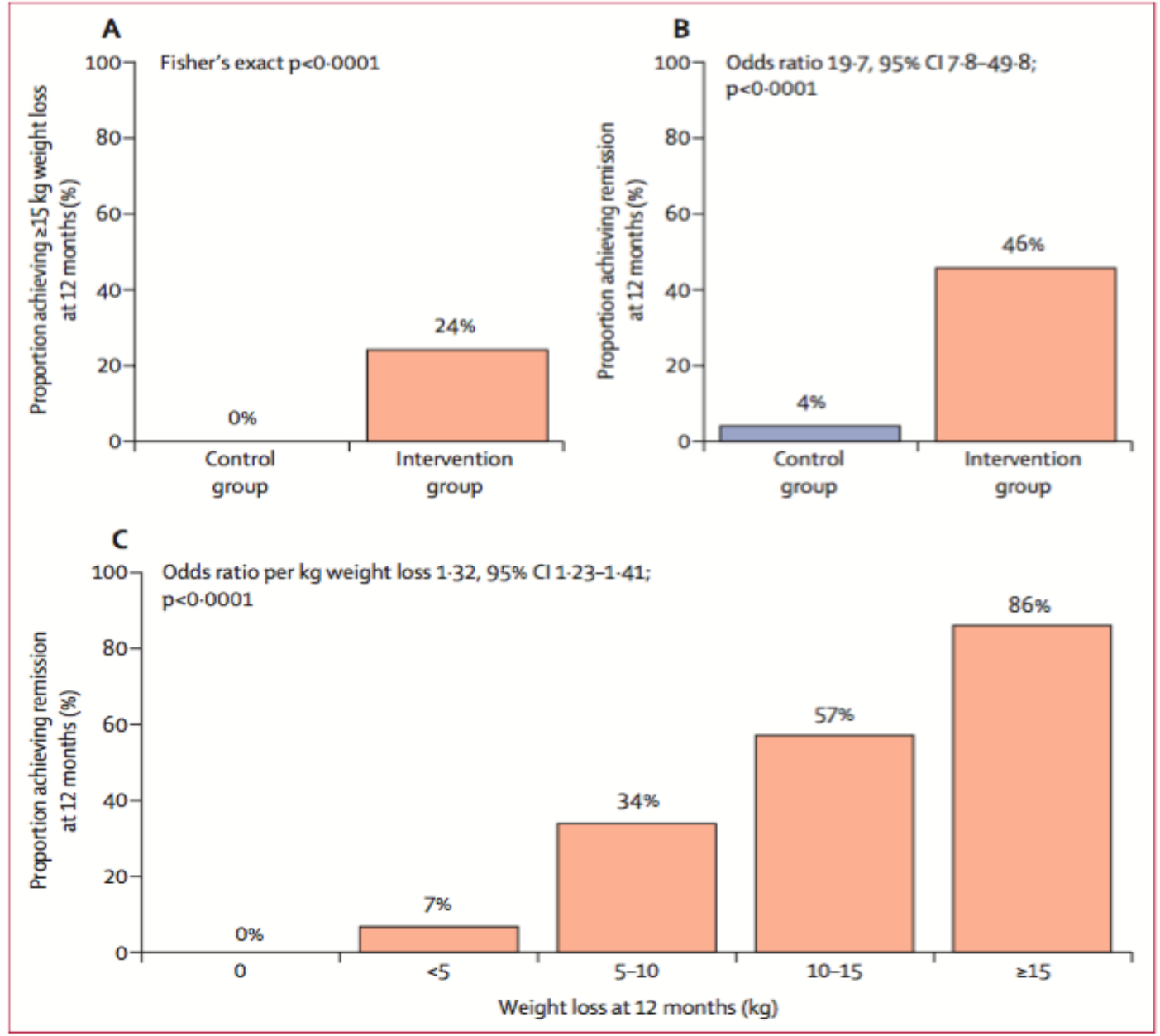

Figure 2: **Primary outcomes and remission of diabetes in relation to weight loss at 12 months**
(A) First co-primary outcome: achievement of at least 15 kg weight loss at 12 months. (B) Second co-primary outcome: remission of diabetes (glycated haemoglobin <6·5% [48mmol/mol], off antidiabetic medication for 2 months). (C) Remission of diabetes, in relation to weight loss achieved at 12 months (both groups combined).

Theresa, 28

- Weight 237kg, height 167cm, BMI 84kg/m2, EOSS 1, class 3

- Referred from bariatric team
  - ***To heavy for surgery (needs to lose approx. 60-70kg)***
- Recent diagnosis of type 2 diabetes , HbA1c 51mmol/mol
- Weight problem longstanding and gradual increase, significant impact on QOL

- Emotional eating and food as reward, night time eating and binge eating, not full after meals (hungry 1-2 hours after large meal)

- Time and financial constrains (fast-food)
- Previously tried to lose weight exercise and team challenges
- Iron deficiency, mild NAFLD, **Vitamin D deficiency**

Theresa, 28

A. Start meal replacements with nutritionally complete product

B. Send to psychology for counseling

C. Start Duromine 15mg and increase to 30mg if tolerated

D. Start weight neutral or weight losing diabetes medications

E. MDT approach with the bariatric surgeons

F. Consider additional weight management medications as part of the MDT – Orlistat, Contrave™ (Bupropion& Naltrexone), Qysimia™ (Duromine & Topiramate)

G. All of the above

Theresa, 28

A. Start meal replacements with nutritionally complete product

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G. All of the above

Theresa, 28

Key aspects:

- **EOSS 1,** Obesity class 3, BMI 84kg/m2, few complications
- Ideal candidate for bariatric surgery but need to lose 60kg prior to surgery

- *What is the difference between case one and case two?*

- *What can do done to prepare her for bariatric surgery?*

Theresa, 28

What cane be done:

1. MDT (medical, dietitian, psychologist)

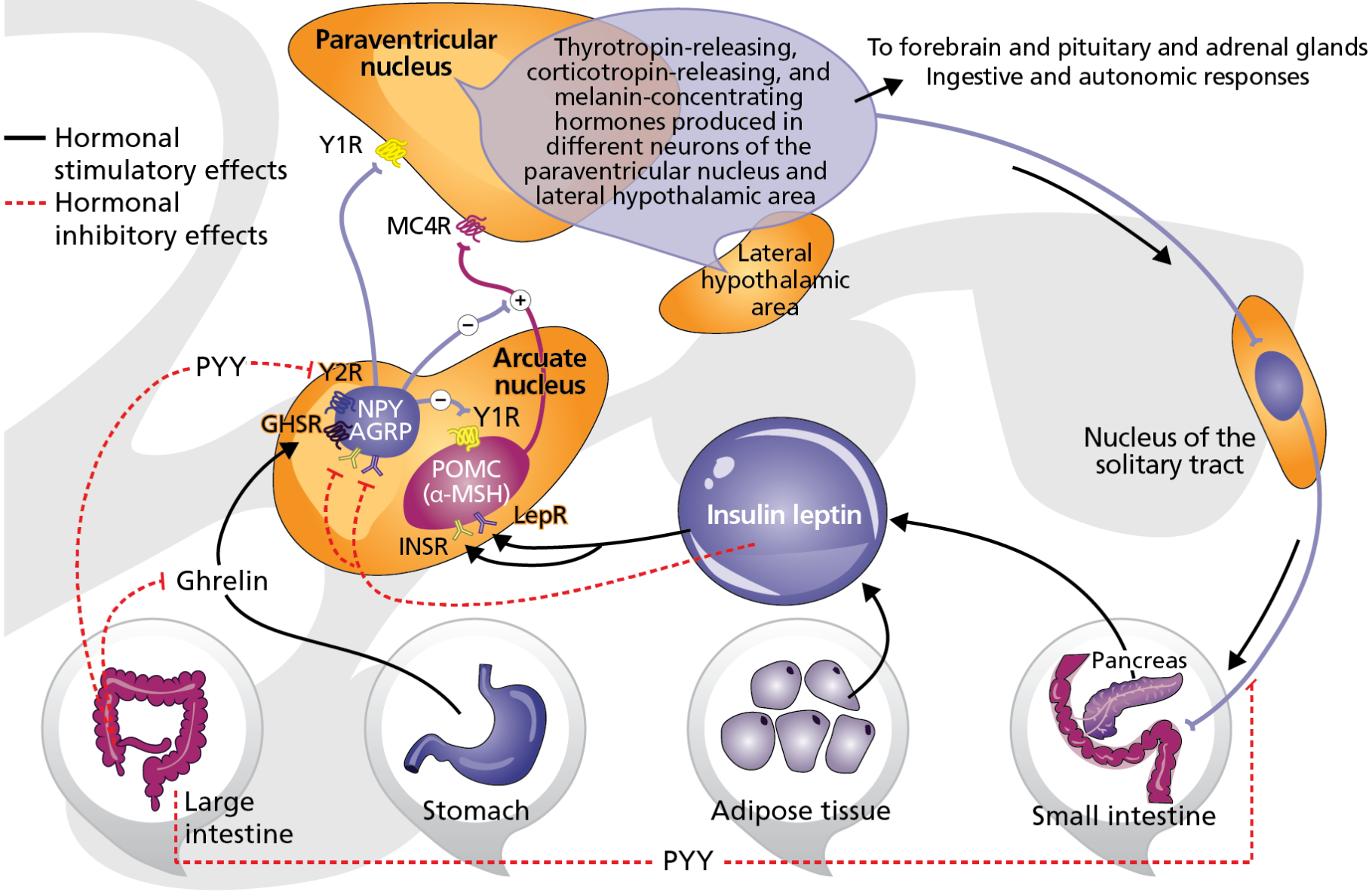
2. Low Calorie Diet (LCD) with nutritionally complete product for at least 8-12 weeks

3. Supported by Duromine, Metformin, Orlistat, other weight management medications – for limited and pre-specified period with clearly outcome measure

4. Beck diet plan (CBT) and stress management techniques

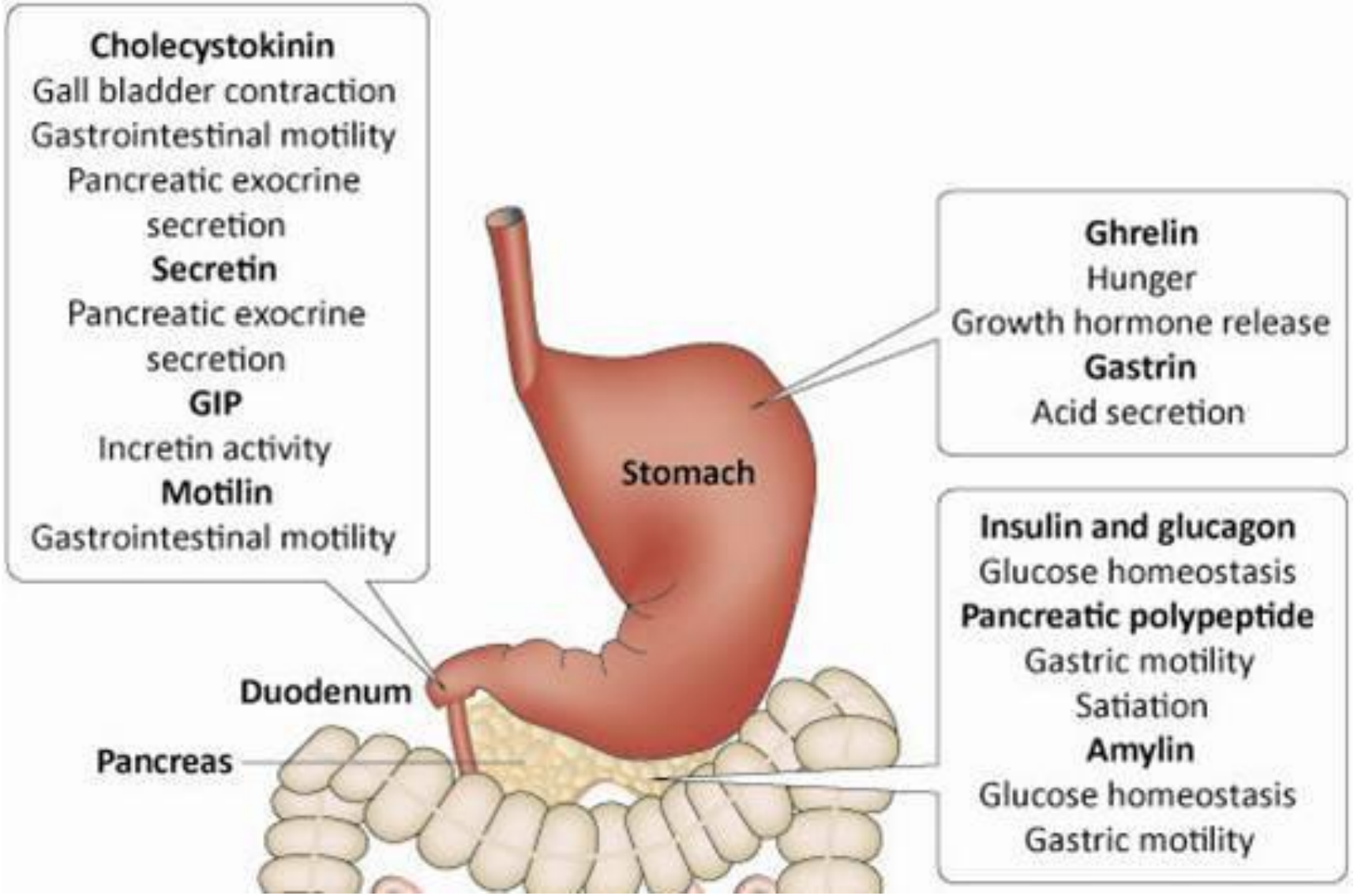
5. CPAP for OSA (respiratory)

Obesity = a brain disease - Control Over Appetite Regulation



AGRP: agouti-related peptide; α-MSH: α-melanocyte-stimulating hormone; GHSR: growth hormone secretagogue receptor; INSR: insulin receptor; LepR: leptin receptor; MC4R: melanocortin-4 receptor; NPY: neuropeptide Y; POMC: proopiomelanocortin; PYY: peptide YY; Y1R; neuropeptide Y1 receptor; Y2R: neuropeptide Y2 receptor. Apovian CM, Aronne LJ, Bessesen D et al. *J Clin Endocrinol Metab*. 2015;100:342-362.

Gut Peptides That Regulate Appetite



Murphy KG, Bloom SR. *Nature*. 2006;444:854-859.

Medications:

Phentermine (Duromine™)

Mechanism of action and pharmacokinetics

- Phentermine is a **sympathomimetic** amine chemically related to amphetamine with significant anorectic activity and effects on the **dopaminergic and noradrenergic nervous systems**
- Appetite suppressant action of phentermine - through the hypothalamus
- Phentermine absorption from the resin complex formulation is slower and peak blood concentration is decreased but prolonged, compared with the same dose of phentermine hydrochloride
- Phentermine is readily absorbed from the gastrointestinal tract and excreted substantially in urine
- The half-life of phentermine is about **25 hours**

Phentermine safety

Cardiovascular effects

increases blood pressure and heart rate, exposing patients to greater cardiovascular risk

blood pressure reduction is related to weight loss - in the **first days after phentermine initiation blood pressure can rise**

1. **Avoid in patients with established CV disease**
2. **Phentermine as a weight maintenance medication**
3. **Low dose treatment with slow titration**
4. **Specialized in obesity management (PC)**
5. **Consult the data sheet**

NEW ZEALAND DATA SHEET

DUROMINE ®

1 PRODUCT NAME

DUROMINE 15 mg capsules

DUROMINE 30 mg capsules

Phentermine plus topiramate combination therapy (EQUIP and CONQUER) - early slight increase in **heart rate** (mean 1.3 +/- 10.3 beats per minute), which was significant only in the **15/92mg** combination

Phentermine evidence

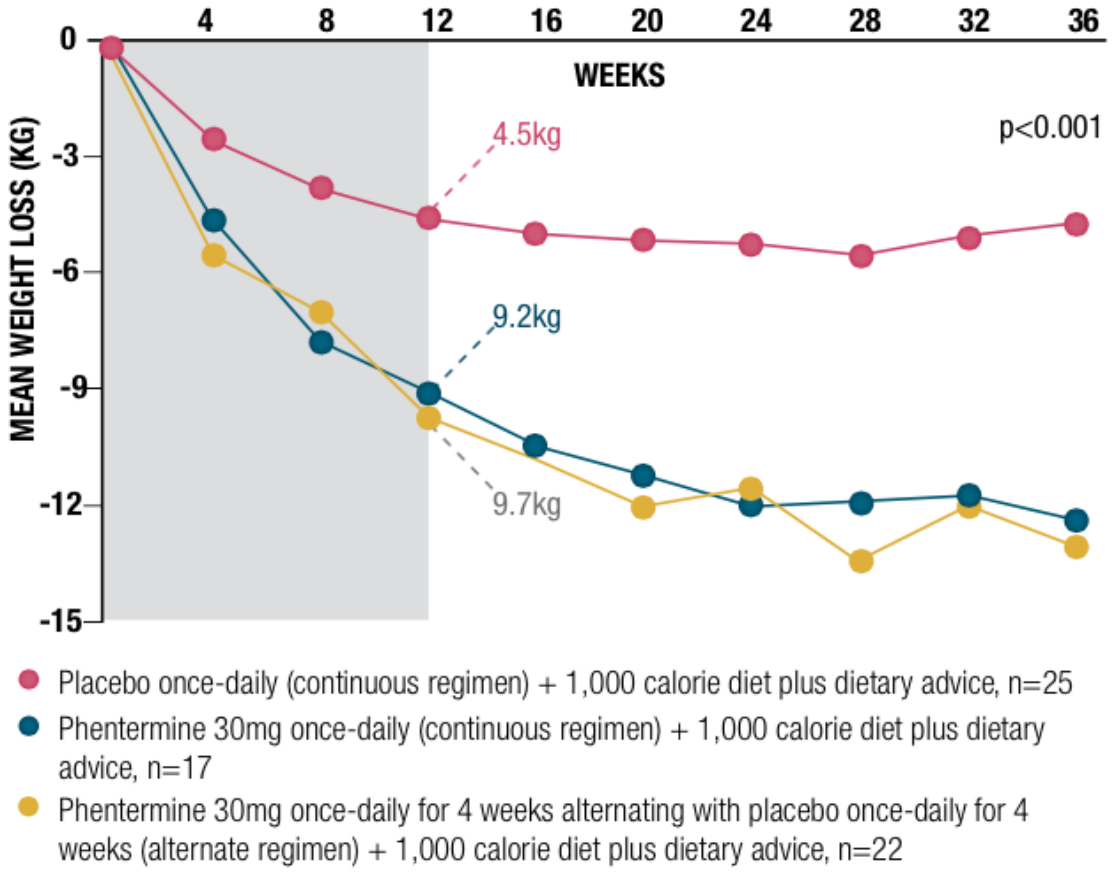


Figure 4. Cumulative mean weight reduction with phentermine vs placebo.[25]

- Phentermine is the most commonly used drug in the treatment of obesity and has been in widespread use for over 55 years

First approved by the US FDA in 1959 (history of anorectics, including phentermine – Colman)

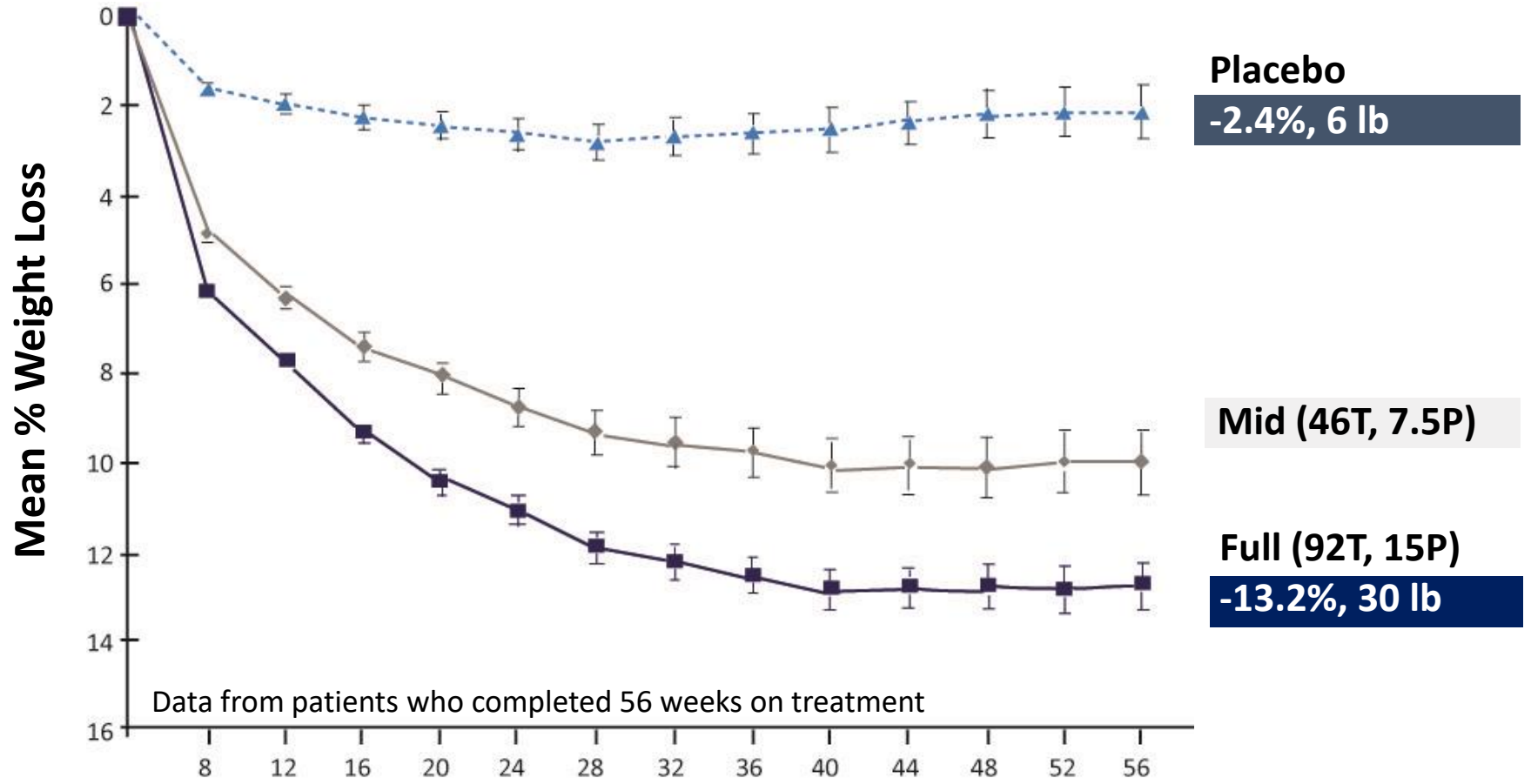
Most of the initial clinical trials, done in the 1950's and 60's, were of relatively short duration and involved small cohorts

ONE long-term, double-blind, randomized controlled phentermine trial: 108 obese women received placebo, continuous phentermine (30 mg/day) or intermittent phentermine (4 weeks on and 4 weeks off) for 36 weeks.

Weight loss was significantly greater in the continuous (12.2kg) and intermittent (13.0kg) groups versus placebo (4.8kg; $p<0.001$) (Figure 4)

CONQUER: Weight Loss Over Time

(Phentermine / Topiramate)



Patients	Placebo	Mid	Full
Completers (% of randomized)	564 (57%)	344 (69%)*	634 (64%)*

*Statistically greater number of patients completing study on combination drug vs placebo, $P < .0001$

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