New Drugs in the Management of Obesity

Dr Joan Khoo
Department of Endocrinology
Changi General Hospital
Anti-obesity drugs

- BMI >30 kg/m\(^2\)
- or BMI >27 kg/m\(^2\) with > 1 comorbid condition (e.g. hypertension, dyslipidemia, T2DM, OSA) who are motivated to lose weight

- Adjunct to reduced-calorie diet and regular exercise

- History of being unable to successfully lose and maintain weight
"I GUARANTEE YOUR APPETITE WILL BE SUPPRESSED IF YOU TAKE ONE OF THESE DIET PILLS PER DAY"
Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline

J Clin Endocrinol Metab, February 2015, 100(2):342–362

Caroline M. Apovian, Louis J. Aronne, Daniel H. Bessesen, Marie E. McDonnell, M. Hassan Murad, Uberto Pagotto, Donna H. Ryan, and Christopher D. Still

Boston University School of Medicine and Boston Medical Center (C.M.A.), Boston, Massachusetts 02118; Weill-Cornell Medical College (L.J.A.), New York, New York 10065; Denver Health Medical Center (D.H.B.), Denver, Colorado 80204; Brigham and Women’s Hospital (M.E.M.), Boston, Massachusetts 02115; Mayo Clinic, Division of Preventative Medicine (M.H.M.), Rochester, Minnesota 55905; Alma Mater University of Bologna (U.P.), S. Orsola-Malpighi Hospital Endocrinology Unit, 40138 Bologna, Italy; Pennington Biomedical Research Center (D.H.R.), Baton Rouge, Louisiana 70808; and Geisinger Health Care System (C.D.S.), Danville, Pennsylvania 17822
### Pharmacotherapy for Obesity

**Available in Singapore (June 2016)**

<table>
<thead>
<tr>
<th>Drug (Generic)</th>
<th>Dosage</th>
<th>Mechanism of Action</th>
<th>Weight Loss Above Diet and Lifestyle Alone, Mean Weight Loss, % or kg²; Duration of Clinical Studies</th>
<th>Status</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine resin</td>
<td>AdipexP</td>
<td>Norepinephrine-releasing agent</td>
<td>3.6 kg (7.9 lb); 2–24 wk</td>
<td>Approved in 1960s for short-term use (3 mo)</td>
<td>Headache, elevated BP, elevated HR, insomnia, dry mouth, constipation, anxiety</td>
</tr>
<tr>
<td></td>
<td>(37.5 mg),</td>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular: palpitation, tachycardia, elevated BP, ischemic events</td>
</tr>
<tr>
<td></td>
<td>37.5 mg/d</td>
<td></td>
<td></td>
<td></td>
<td>Central nervous system: overstimulation, restlessness, dizziness, insomnia, euphoria,</td>
</tr>
<tr>
<td></td>
<td>Ionamin (30 mg),</td>
<td></td>
<td></td>
<td></td>
<td>dysphoria, tremor, headache, psychosis</td>
</tr>
<tr>
<td></td>
<td>30–37.5 mg/d</td>
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<td></td>
<td>Gastrointestinal: dryness of the mouth, unpleasant taste, diarrhea, constipation,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>other gastrointestinal disturbances</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Allergic: urticaria</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Endocrine: impotence, changes in libido</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Decreased absorption of fat-soluble vitamins, steatorrhoea, oily spotting, flatulence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>with discharge, fecal urgency, oily evacuation, increased defecation, fecal incontinence</td>
</tr>
<tr>
<td>Orlistat,</td>
<td>120 mg TID</td>
<td>Pancreatic and gastric lipase inhibitor</td>
<td>2.9–3.4 kg (6.5–7.5 lb), 2.9–3.4%; 1 y</td>
<td>FDA approved in 1999 for chronic weight</td>
<td></td>
</tr>
<tr>
<td>prescription (120 mg)</td>
<td></td>
<td></td>
<td></td>
<td>management</td>
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</tr>
</tbody>
</table>

**Appetite suppressant**

**Steatorrhoea**
Factors in Choosing a Weight Loss Medication

- Is the patient willing to take a weight loss medication?
- What medications is the patient on? Are there drug-to-drug interactions to consider?
- Does the patient have diabetes or is pre-diabetic?
- What is the patient’s medical history?
Integrated gut-brain regulation of appetite

Signals from cortical centres (e.g. for mood, stress, learned behaviour, rewards) integrated with signals in hypothalamus, brainstem and gut to regulate appetite

ARC = arcuate nucleus
PVN = paraventricular nucleus
LHA = lateral hypothalamic area
NTS = nucleus tractus solitarius
NPY = neuropeptide Y
POMC = proopiomelanocortin
GLP-1 = glucagon-like peptide 1

Norepinephrine ↓ NPY signaling
Serotonin ↑ POMC production

GLP-1 stimulates satiety
## Summary of appetite suppressants

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
<th>MECHANISM OF ACTION</th>
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<td>GABA-receptor modulator (T)</td>
<td>7-9%</td>
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<td>32/360 mg up to 2 tabs BD</td>
<td>Opioid antagonist (N) Inhibits reuptake of norepinephrine and dopamine (B)</td>
<td>5%</td>
<td>Headache, dry mouth, nausea, constipation, dizziness</td>
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BLOOM (Behavioral modification and Lorcanerin for Overweight and Obesity Management) study

Smith SR et al. NEJM 2010; 363: 245-56
BLOOM study – percentage of patients who lost 5 and 10% of baseline weight

Smith SR et al. NEJM 2010; 363: 245-56
BLOSSOM (Behavioral modification and Lorcaserin Second Study for Obesity Management) Study

BLOOM-DM (Behavioral modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) study

O’Neill PM et al. Obesity (Silver Spring) 2012; 20:1426-36
Behavioural modification in the BLOOM and BLOSSOM studies

- Nutritional and physical exercise counseling were provided at baseline, week 1, 2, and 4; and monthly thereafter.

- Instructed to reduce daily caloric intake to 600 kcal below individual estimated energy requirements.

- Food diaries were used as motivational tools and to assist with counseling sessions.

- Encouraged to exercise moderately for 30 min/day; some already exercising 1 hour/day.
**Lorcaserin – adverse events**

<table>
<thead>
<tr>
<th></th>
<th>BLOOM</th>
<th>Year One</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>Lorcanerin</td>
<td></td>
<td></td>
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<tr>
<td>Headache</td>
<td>18.0%</td>
<td>11.0%</td>
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<tr>
<td>Upper respiratory infection</td>
<td>14.8%</td>
<td>11.9%</td>
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<td>Nasopharyngitis</td>
<td>13.4%</td>
<td>12.0%</td>
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<tr>
<td>Dizziness</td>
<td>8.2%</td>
<td>3.8%</td>
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<tr>
<td>Nausea</td>
<td>7.5%</td>
<td>5.4%</td>
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<tr>
<th></th>
<th>BLOSSOM</th>
<th>Lorcanerin 10 mg BID</th>
<th>Lorcanerin 10 mg QD</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Headache</td>
<td>15.6%</td>
<td>15.6%</td>
<td>9.2%</td>
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<td>12.7%</td>
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Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP)

Dose-dependent effect of phentermine/topiramate on weight loss = 5-10% compared to 1% with placebo

2/3 of subjects lost > 5% of weight with P/T 15/92

Greater reductions in BP, FPG, chol, TG and LDL compared to placebo
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Weight Loss With Naltrexone SR/Bupropion SR Combination Therapy as an adjunct to Behavior Modification: The COR-BMOD Trial

Weight loss with Naltrexone/Bupropion in the COR-BMOD Trial

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Weight loss with diabetic meds

Dual therapy
- Efficacy: Intermediate
- Hypo risk: Low risk
- Weight: Neutral
- Side effects: Rare
- Costs: High

Triple therapy
- DPP-4 inhibitor + SU
- or TZD
- or SGLT2-i
- or Insulin
- Metformin
- LIRAGLUTIDE

LIRAGLUTIDE
- high
- low risk
- loss
- GI
- high

Metformin
- SGLT2 inhibitor
- intermediate
- low risk
- low risk
- dehydration
- high

Metformin
- DPP-4 inhibitor
- high
- low risk
- loss
- GI
- high

LIRAGLUTIDE
- high
- low risk
- loss
- GI
- high
Weight loss with liraglutide in obese people

Weight loss over 1 year in obese people with or without diabetes

Astrup et al. Lancet 2009; 374 (901): 1606-16
Weight loss with liraglutide in obese adults

- 846 T2DM with BMI ≥ 27.0 and HbA1c 7.0-10.0% on diet or up to 3 OHA (metformin, SU, TZD) with stable body weight

- Weight loss 4.7% (5 kg) and 6.0% (6.4 kg) with 1.8 and 3 mg of liraglutide, compared to 2% (2.2 kg) with placebo

- Weight loss > 5% in 40-55% of liraglutide group vs. 20% of placebo group

Davies MJ et al for the SCALE Diabetes RCT. JAMA 2015; 3414: 687-99
A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

- 3731 non-diabetic patients with BMI ≥ 30 or a BMI ≥ 27 with dyslipidemia or hypertension

- Once-daily SC liraglutide 3.0 mg (n = 2487) or placebo (n = 1244)

- Both groups received counseling on lifestyle modification

- Mean (±SD) age of the patients was 45.1 ± 12.0 years, mean weight was 106.2 ± 21.4 kg, and the mean BMI was 38.3 ± 6.4

Weight loss with Liraglutide 3 mg daily in non-diabetic adults

2/3 of patients lost at least 5% of baseline weight with liraglutide, and 1/3 lost at least 10%

Weight loss was 8.4 kg with liraglutide, compared with 2.8 kg with placebo at 56 weeks

Weight loss with SGLT-2 inhibition in type 2 diabetic patients on metformin and insulin.

When to stop?

• If the patient has not lost $\geq 5\%$ of their baseline weight in 3/12:
  → try another medication
  → increase the dose if applicable

• If positive results, continue for at least 6-12 months
Eating less eventually leads to more regain

**Persistent Metabolic Adaptation 6 Years After “The Biggest Loser” Competition**

Erin Fothergill, Juen Guo, Lilian Howard, Jennifer C. Kerns, Nicolas D. Knuth, Robert Brychta, Kong Y. Chen, Monica C. Skarulis, Mary Walter, Peter J. Walter, and Kevin D. Hall

**Results:** Of the 16 “Biggest Loser” competitors originally investigated, 14 participated in this follow-up study. Weight loss at the end of the competition was (mean ± SD) 58.3 ± 24.9 kg ($P < 0.0001$), and RMR decreased by 610 ± 483 kcal/day ($P = 0.0004$). After 6 years, 41.0 ± 31.3 kg of the lost weight was regained ($P = 0.0002$), while RMR was 704 ± 427 kcal/day below baseline ($P < 0.0001$) and metabolic adaptation was $-499 ± 207$ kcal/day ($P < 0.0001$). Weight regain was not significantly correlated with metabolic adaptation at the competition’s end ($r = -0.1$, $P = 0.75$), but those subjects maintaining greater weight loss at 6 years also experienced greater concurrent metabolic slowing ($r = 0.59$, $P = 0.025$).

**Conclusions:** Metabolic adaptation persists over time and is likely a proportional, but incomplete, response to contemporaneous efforts to reduce body weight.
Metabolic adaptation after weight loss
# Medications Known To Be Associated With Drug-Induced Weight Gain

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Tricyclic antidepressants, MAOIs, SSRIs (paroxetine), mirtazapine</td>
</tr>
<tr>
<td>Diabetes therapy</td>
<td>Insulin, sulfonylureas, thiazolidinediones</td>
</tr>
<tr>
<td>Contraceptive drugs</td>
<td>Birth control injections and devices (medroxyprogesterone acetate injectable suspension, levonorgestrel-releasing intrauterine system)</td>
</tr>
<tr>
<td>Antipsychotic agents</td>
<td>Phenothiazines, olanzapine, clozapine, risperidone</td>
</tr>
<tr>
<td>Antiepileptic agents</td>
<td>Gabapentin, pregabalin, valproic acid, vigabatrin, carbamazepine</td>
</tr>
<tr>
<td>Other</td>
<td>Lithium, steroid hormones, beta- and alpha-1 adrenergic receptor blockers, HIV protease inhibitors (increase deposition of visceral adipose tissue, lipodystrophy)</td>
</tr>
</tbody>
</table>

Response vs Nonresponse to Weight Loss Medications

In clinical trials

- Weight loss of approximately 5% or more within the first several months of treatment predicted a longer-term response (approximately 5% to 10% at 1 year)
- Weight loss of less than 5% within the first several months of treatment predicted longer-term nonresponse (<5% at 1 year)

These patterns can guide clinical use of medications

Summary

- Individualize weight loss medications to patients

- Patients who do best are those who are making a concerted effort to lose weight but are not seeing the desired results on their own

- DRUGS ALONE DO NOT WORK!
Which of these weight loss drugs does not suppress appetite?

A) Lorcaserin
B) Phentermine/Topiramate
C) Naltrexone/Bupropion
D) Orlistat
E) Liraglutide
Adverse effects of appetite suppressants include all except:

A) Dizziness
B) Headache
C) Dry mouth
D) Constipation
E) Oily frequent stools
Which statement is false?

A) New weight-loss medications reduced weight by an average of 5-10% in clinical studies
B) GLP-1 agonists and SGLT-2 inhibitors are useful adjuncts for weight loss in type 2 diabetic patients
C) Antipsychotic, antiepileptic and antidepressant medications are associated with weight gain
D) Weight loss < 5% within 3/12 of treatment predicts better weight loss at 1 year