Medicating the Patient with Obesity... Clinical Roadmap

Grand Rounds – Bend, Oregon

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Objectives

At the end of the presentation, attendees will be able to discuss the following issues related to management of the patient with obesity:
1. Appropriate management of medications that promote weight gain;
2. Best practices in prescribing for medications approved for chronic weight management;
3. Safety and efficacy profiles of those medications; and
4. Incorporating a plan for weight management specific to your office.

Disclosure

Dr. Ryan has received financial remuneration in 2015 from Amgen, Novo Nordisk, Janssen, Pfizer, Takeda, Vivus, Real Appeal, and Scientific Intake.

Let’s start with a case study....

Carmella Z. 44 year old nurse anesthetist, history of HTN; referred by boss for evaluation; job performance is suffering. She is divorced and has two kids at home (8 and 12).
• CC: “tired all the time” and “I am almost dropping off at work”

• Physical Examination: Height 65 inches, weight 225 pounds, BMI 37. Blood pressure 145/90. The physical examination is normal. Pap smear obtained and mammogram ordered.

• Meds: depot progesterone for contraception, propranolol and hydrochlorothiazide for HTN, acetaminophen PM for sleep, oxybutynin for incontinence

• Labs: Chem profile: Fasting glucose 117, A1c 5.9% TG 170 mg/dL, otherwise chem survey, lipid panel normal.

• SH: Divorced, 2 kids at home (8 and 12)

• History: weighed 130 pounds when she finished college
  – gained about 15 pounds when she quit smoking
  – gained “40 pounds with each of her three pregnancies and “had to fight to lose the most of the extra weight afterwards”
  – divorced five years ago, experienced depression, took paroxetine and gained 30 pounds.
  – Lost 25 pounds with Jenny Craig and 15 pounds with Weight Watchers – with regain.
  – “I know how to diet, but not how to keep it off. I go to water aerobics at the Y once a week. My knees give me problems when walking or jogging.”

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Which one of the patient’s medications (present and past) is not likely to have contributed to her weight gain?

1. Oxybutynin ★
2. Paroxetine
3. Depot progesterone
4. Propanolol
5. Acetaminophen PM

Message: Consider iatrogenic weight gain.

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Which aspect of the patient’s history is not likely to have contributed to her weight gain and failure to maintain weight loss?

1. Smoking cessation
2. Shift work and sleep deprivation
3. Post-partal weight retention
4. Sedentary lifestyle
5. Jenny Craig and Weight Watchers ★

Message: There are risk factors for weight gain. Regain is biologically driven. It is not all about will power.

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What additional information is most important to obtain before undertaking a treatment plan?

1. Liver biopsy
2. Sleep study ★
3. Beck Depression Inventory
4. X rays of knees and orthopedic evaluation
5. Repeat lipid profile and fasting glucose

Message: To be successful with weight loss, you must address sleep deprivation, chronic disease control (diabetes, OSA), depression and other psychology factors.
What is your clinical roadmap for Ms. Z?

- Complications Centric:
  - Evaluate for OSA, likely treat with CPAP; Metformin for prediabetes; fish oil for TG lowering; continue other meds; educate that diet and exercise is a good way to lower risk for diabetes; return in 6 to 12 months.

- Weight Centric:
  - Evaluate for OSA, likely treat with CPAP; coach the patient in developing a weight management plan, with your specific role being the medication management expert.

But you haven’t told us anything about prescribing medications for chronic weight management!

- Successful weight management requires addressing factors that drive weight gain and resistance to weight loss.
- Physicians and other prescribers have the unique responsibility to manage medications for chronic diseases wisely, avoiding the potential for weight gain, wherever possible.

Medications for Diabetes and Weight

<table>
<thead>
<tr>
<th>WEIGHT GAIN ASSOCIATED WITH USE</th>
<th>ALTERNATIVES (WEIGHT REDUCING IN PARENTHESES)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (weight gain differs with type and regimen used)</td>
<td>(Metformin) (Acarbose) (Miglitol) (Pramlintide) (Exenatide) (Liraglutide) (SGLT 2 inhibitors)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones Sitagliptin? Metiglinide</td>
<td></td>
</tr>
</tbody>
</table>

* Only liraglutide 3.0 is FDA approved for chronic weight management in patients with BMI 30+ kg/m² or BMI 27 <30 kg/m² with one or more comorbidities.

Antidepressant Medications and Weight

<table>
<thead>
<tr>
<th>WEIGHT GAIN ASSOCIATED WITH USE</th>
<th>ALTERNATIVES (WEIGHT REDUCING IN PARENTHESES)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants/mood stabilizers: tricyclic antidepressants</td>
<td>Amytriptyline Dextroprin Imipramine Nortriptyline Trimipramine Mirtazapine</td>
</tr>
<tr>
<td>Antidepressants/mood stabilizers: SSRIs</td>
<td>Fluoxetine Sertraline Paroxetine Fluvoxamine</td>
</tr>
<tr>
<td>Antidepressants/mood stabilizers: MAO Inhibitors</td>
<td>Phenylzine Tranylcypromine</td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
</tr>
</tbody>
</table>

* Only naltrexone SR/bupropion SR combination is FDA-approved for chronic weight management in patients with BMI 30+ kg/m² or BMI 27 <30 kg/m² with one or more comorbidities.

### Cardiologic Medications and Weight

<table>
<thead>
<tr>
<th>Hypertension Medications</th>
<th>WEIGHT GAIN ASSOCIATED WITH USE</th>
<th>ALTERNATIVES (WEIGHT REDUCTING IN PARENTHESES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors?</td>
<td></td>
<td>Calcium channel blockers?</td>
</tr>
<tr>
<td>Calcium channel blockers?</td>
<td></td>
<td>Angiotensin-2 receptor antagonists</td>
</tr>
</tbody>
</table>


### Antipsychotic and Anticonvulsant Medications and Weight

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>WEIGHT GAIN ASSOCIATED WITH USE</th>
<th>ALTERNATIVES (WEIGHT REDUCTING IN PARENTHESES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td></td>
<td>Risperidone</td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td></td>
<td>Aripiprazole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>WEIGHT GAIN ASSOCIATED WITH USE</th>
<th>ALTERNATIVES (WEIGHT REDUCTING IN PARENTHESES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td></td>
<td>Lamotrigine?</td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
<td>(Topiramate)</td>
</tr>
<tr>
<td>Valproate</td>
<td></td>
<td>(Zonisamide)</td>
</tr>
</tbody>
</table>

* Only phentermine/topiramate ER is FDA-approved for chronic weight management in patients with BMI ≥30 kg/m² or BMI 27 <30 kg/m² with one or more comorbidities


### Gynecologic Medications and Weight

<table>
<thead>
<tr>
<th>Oral Contraceptives</th>
<th>WEIGHT GAIN ASSOCIATED WITH USE</th>
<th>ALTERNATIVES (WEIGHT REDUCTING IN PARENTHESES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestational</td>
<td>Barrier methods</td>
<td>IUDs</td>
</tr>
<tr>
<td>Steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progestational</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids containing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progestational</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids containing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depot leuprolide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### How do I make this actionable in my office?

- You are already gathering data on medications at every visit.
- Review medications. Consider alternatives if there are weight gain issues.
- Inform patients before prescribing about potential for weight gain. Patient should be part of the informed decision making process.
**Why would I want to prescribe a medication approved for chronic weight management?**

These modern medications have been shown to safely

- produce more weight loss than lifestyle modification alone,
- increase the chances that patients will have weight loss that is associated with improvements in health indices, and
- maintain weight loss over the long term.

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**Weight loss may improve obesity related comorbidities**

![Diagram showing benefits of weight loss reduction: Reduction in risk of Type 2 diabetes, Reduction in cardiovascular risk factors, Improvements in lipid profile, Improvements in blood pressure, Improvements in severity of obstructive sleep apnoea, Improvements in health-related quality of life.]

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**Modest Weight Loss Has Benefits, with Greater Weight Loss Associated with Greater Benefit**

- Measures of glycemia\(^1\)
- Triglycerides\(^2\) and HDL cholesterol\(^2\)
- Systolic and diastolic blood pressure
- Hepatic steatosis measured by MRS\(^2\)
- Measures of feeling and function:
  - Symptoms of urinary stress incontinence\(^6\)
  - Measures of sexual function\(^3\)
  - Quality of life measures (IWQOL)\(^4\)
- NASH Activity Score measured on biopsy\(^3\)
- Apnea-hypopnea index\(^4\)
- Reduction in CV events, mortality, remission of T2DM

\(^{-3.0\%}\)\(^{-5.0\%}\)\(^{-10.0\%}\)\(^{-15.0\%}\)

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**Best Practices in Prescribing Medications for Chronic Weight Management**

1. Follow the label: indicated for
   - BMI 40+ or 35<40 with comorbidity (patients who need to lose weight for health reasons)
   - patients who have history of struggle
   - improving adherence to diet and physical activity (always prescribe as part of a lifestyle regimen).
2. Do no harm: know warnings and contraindications.
3. Consider secondary benefits of medications.
4. Use shared decision making in choosing a medicine.
5. Evaluate efficacy at ~3 months, continue for long term use, like other meds for chronic disease.

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1. Wing et al. Diabetes Care 2013;36:1481-1486
2. Loos et al. Diabetes Care 2012;35:1534-1543
6. Wing et al. Diab Care 2010;33:2156-2163
Medications approved for chronic weight management and how they work

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/


<table>
<thead>
<tr>
<th>Agent &amp; Agent Action</th>
<th>Approval Date</th>
<th>Scheduled Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat/Xenical™</td>
<td>Approved 1997</td>
<td>No</td>
</tr>
<tr>
<td>Lorcaserin/Belviq®</td>
<td>Approved 2012</td>
<td>Yes</td>
</tr>
<tr>
<td>Phentermine/Topiramate ER Qsymia™</td>
<td>Approved 2012</td>
<td>Yes</td>
</tr>
<tr>
<td>Naltrexone SR/Bupropion SR Contrave®</td>
<td>Approved 2014</td>
<td>No</td>
</tr>
<tr>
<td>Liraglutide 3.0 mg Saxenda®</td>
<td>Approved 2014</td>
<td>No</td>
</tr>
</tbody>
</table>

Let’s talk about efficacy...

- FDA efficacy bench marks for approval:
  >5% weight loss than placebo
  at least 35% of those on medications achieve 5% weight loss and twice as many as on placebo

All approved medications have approximated or exceeded these bench marks.

Placebo-subtracted Weight Loss in Patients With and Without T2DM

These are not head to head comparisons, are composed of different patient populations and one should not infer superiority or inferiority. All medications have approximated the FDA efficacy criteria.

When individual weight loss is displayed, it looks like this:

Proportion (%) achieving 5% weight loss after 52 weeks at top dose

<table>
<thead>
<tr>
<th>Medications approved for chronic weight management</th>
<th>Dosing</th>
<th>Response Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>120 mg orally with each meal</td>
<td>Not addressed in label</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>20 mg orally twice daily</td>
<td>Stop if &gt;5% loss at 12 weeks</td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>Daily in am, 3.75 mg/75 mg x 14 days, then 7.5 mg/150 mg x 14 days</td>
<td>At 12 weeks, option to ↑ to 11.25 mg/150 mg x 14 days, then 15 mg/187.5 mg, Stop if &lt;5% loss at 12 weeks or any change</td>
</tr>
<tr>
<td>Naltrexone SR/Bupropion SR</td>
<td>Oral/IV: Wk 1-4: 150/150 mg bid 1st am; Wk 1 - 1st am 1st pm; Wk 2 - 2 pm 2 pm; Wk 3 - 2 pm 2 pm; Wk 4 - 2 pm 2 pm</td>
<td>Stop if &lt;5% loss at 12 weeks</td>
</tr>
<tr>
<td>Liraglutide 3 mg</td>
<td>Inject subcutaneously any time of day; Wk 1-4: 0.6 mg; increase dose by 0.6 mg weekly until dose is 3.0 mg (Wk 5)</td>
<td>Stop if &lt;5% weight loss at 56 weeks</td>
</tr>
</tbody>
</table>

All data from product label

Proportion (%) achieving 10% weight loss after 52 weeks at top recommended dose

<table>
<thead>
<tr>
<th>Medications approved for chronic weight management – data from prescribing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
</tr>
<tr>
<td>Orlistat</td>
</tr>
<tr>
<td>Lorcaserin</td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
</tr>
<tr>
<td>Naltrexone SR/Bupropion SR</td>
</tr>
<tr>
<td>Liraglutide 3 mg</td>
</tr>
</tbody>
</table>

All data from product label

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### Medications Approved for Chronic Weight Management – Tolerability

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>All the symptoms of stratorhoea (fatty discharge, etc.)</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Headache, dizziness, fatigue</td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>Paresthesias, dysgeusia, dizziness, dry mouth</td>
</tr>
<tr>
<td>Naltrexone SR/ Bupropion SR</td>
<td>Nausea, vomiting, headache, dizziness, insomnia</td>
</tr>
<tr>
<td>Liraglutide 3 mg</td>
<td>Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain</td>
</tr>
</tbody>
</table>

All data from product label

### Medications Approved for Chronic Weight Management – Safety and Contraindications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Safety</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Warning: Cholinergic nervous system; tape, bone fracture; multivitamins;</td>
<td>Chronic myasthenia; gall bladder disease</td>
</tr>
<tr>
<td></td>
<td>Headaches; dizziness; fatigue; headache; dizziness; dry mouth</td>
<td></td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Warning: Hypothalamic dysfunction; cardiovascular disease; cognitive</td>
<td>Do not use with MAOIs; Use with &quot;contraceptive solution&quot; with acute sympathetics (SSRls, SNRIs); Pregnancy</td>
</tr>
<tr>
<td></td>
<td>impairment; depression; hypopharyngeal, pharynx;</td>
<td></td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>Warning: fetal toxicity; acute myopia; cognitive dysfunction; metabolic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormalities; hypertension; dyspepsia; hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Naltrexone SR/ Bupropion SR</td>
<td>Warning: Hypothalamic dysfunction; cardiovascular disease; cognitive</td>
<td>Do not use with MAOIs; Use with &quot;contraceptive solution&quot; with acute sympathetics (SSRls, SNRIs); Pregnancy</td>
</tr>
<tr>
<td></td>
<td>impairment; depression; hypopharyngeal, pharynx;</td>
<td></td>
</tr>
<tr>
<td>Liraglutide 3.0 mg</td>
<td>Bladder, nausea, vomiting, headache, constipation, dyspepsia, abdominal</td>
<td>Patients with personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia (MEN); Pregnancy</td>
</tr>
<tr>
<td></td>
<td>pain</td>
<td></td>
</tr>
</tbody>
</table>

All data from product label

### Medications for Chronic Weight Management and the Patient

- Pregnancy
- Breastfeeding
- Seizure history
- Hypertension
- Kidney stones
- Glaucoma
- Diabetes

All data from product label
Medications for Chronic Weight Management and the Patient

- Pregnancy
- Breastfeeding
- Seizure history
- Kidney stones
- Glaucoma
- Hypertension

- Arrhythmia
- Renal impairment
- Hepatic impairment
- Depression
- Pancreatitis
- Medullary thyroid cancer
- MEN II
- Age >65
- Pancreatitis
- Depression
- Medullary thyroid cancer

For patients with history of seizures:
• naltrexone SR/bupropion SR is contraindicated
• Taper phentermine/topiramate ER slowly when discontinuing

For patients with history of kidney stones:
• orlistat can increase risk
• phentermine/topiramate ER can increase risk

For patients with glaucoma:
• phentermine/topiramate ER is contraindicated
• naltrexone SR/bupropion SR is associated with angle closure glaucoma

All data from product label
For patients with hypertension:
- naltrexone SR/bupropion SR can increase blood pressure
- phentermine/topiramate ER can increase blood pressure

For patients with arrhythmia:
- phentermine/topiramate ER, naltrexone SR/bupropion SR, and liraglutide can increase heart rate.

For patients with hepatic impairment:
- DO NOT EXCEED: 7.5 mg/46 mg phentermine/topiramate ER
- DO NOT EXCEED: 8 mg/90 mg naltrexone SR/bupropion SR
- USE WITH CAUTION: orlistat, liraglutide
- NO INFORMATION: lorcaserin

All data from product label
For patients with a history of glaucoma or pregnancy/breastfeeding, all has been studied in patients.

For patients on SSRIs, SNRIs:
- Use lorcanarin with caution
- Use naltrexone SR/bupropion SR with caution
- Do not use orlistat, XLS/M的教学, or phentermine/topiramate ER.

All data from product label.

For patients with history of pancreatitis:
- • Prescribe liraglutide with caution.

For patients with personal history or family history of medullary thyroid carcinoma or MEN II:
- • Liraglutide is contraindicated.

For patients over age 65:
- • Some, limited experience with liraglutide, phentermine/topiramate ER, bupropion, and naltrexone SR/bupropion SR.
- • No experience with orlistat.

All data from product label.
Developing a Weight Centric Approach in YOUR office

- What is YOUR role?
  - Raise the issue
  - Keep patients engaged, or at least returning

Developing a Weight Centric Approach in YOUR office

- Wise prescribing: Download (FREE!) ENDO Guidance on Medications
- Refer for lifestyle counseling
  - Office extender as trained interventionist, RD with weight management certificate, Nutrisystem, Jenny Craig, Weight Watchers

or become an expert

Where to go for training in Obesity Medicine

Certified Obesity Medicine Physician

<table>
<thead>
<tr>
<th>Year</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Physicians</td>
<td>726</td>
<td>306</td>
<td>435</td>
<td>540</td>
</tr>
</tbody>
</table>
What happened to Carmella Z?

- Diagnosed with severe OSA and started CPAP.
- Daytime sleepiness improved; acetaminophen pm stopped.
- ACE inhibitor started and HCTZ, propranolol stopped. GYN stopped Depot progesterone and barrier method substituted. Paroxetine tapered and stopped without mood alteration.
- She began a meal replacement diet (2 frozen entrees, 2 snacks and one family meal, 1200 kcal/d) for 3 months and then transitioned to a low carb diet with one meal replacement per day. She chose to take liraglutide 3.0 mg, after researching all obesity medications on the internet, and started it when she transitioned to the low carb diet. She got a stationary bike and alternates daily biking and swimming.

Carmella Z. The results....

- She started to lose weight with the medications changes and at the start of her diet she weighed 210 pounds. She lost 20 pounds the first 3 months and an additional 10 pounds over the next 3 months. At one year her new weight was 180 pounds.
- She is normoglycemic and her blood pressure is 132/82. TG 90. Her knee pain is resolved. She no longer takes oxybutynin. She is sleeping well and is questioning whether she needs to continue CPAP. You advise another sleep study before she stops.
- She says, "You know, this has actually benefitted my children. At their last check up they both had decreased their BMI percentile scores! Thank you for pointing me in this direction, doctor. It was hard work, but I made it."
- She has continued on liraglutide 3.0 mg for 3 years and her current weight is 175.

Yes, these results are typical!

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Weight-Loss Maintenance and Loss With Medication After Low-Energy Diet (LED)

![Graph showing weight loss changes over time for different medications.](image)

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Thank You
Objectives

At the end of the presentation, attendees will be able to discuss the following issues related to management of the patient with obesity:

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