Contrave® (naltrexone SR/bupropion SR) for treatment of obesity

With the approval of Contrave®, only four drugs are currently FDA approved for long-term treatment of obesity. The other three are Qsymia® (phentermine/topiramate ER), Belviq® (lorcaserin), and Alli® or Xenical® (orlistat).

**Contrave® summary:**
- 8 mg naltrexone HCl and 90 mg bupropion HCl per tablet
- Dose escalation over the first 4 weeks (see package insert for details)
- Indicated for use only in adults with body mass index (BMI) ≥ 30 kg/m² OR adults with BMI ≥ 27 kg/m² plus at least one weight-related comorbid disease state
- If patient does not lose ≥ 5% of baseline body fat by the 12th week of treatment, discontinue

All four approved obesity agents have unique proposed mechanisms of action in causing weight loss, and all but orlistat work through various CNS pathways. The table on page 5 is a brief overview of Contrave® and Qsymia® to highlight differences between the medications.

One phase III trial demonstrated the potential for 9.3% weight loss from baseline when Contrave® was combined with behavioral modification support. None of the obesity treatments are maximally effective without diet and exercise, but Contrave® and Qsymia® have higher weight loss potential than the other agents.

**Contrave® warnings**
- Contraindicated in combination with opioids, other bupropion-containing products, and MAOIs
- Contraindicated in uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, and when discontinuing alcohol, benzodiazepines, barbiturates, or antiepileptic drugs
- Pregnancy category X—no maternal benefit and possible fetal harm from weight loss, but is not teratogenic
- Not recommended while breastfeeding—active ingredients can be secreted in breast milk
- Black box warning of suicidal behavior and ideation due to bupropion
- Black box warning of serious neuropsychiatric reactions in patients also attempting smoking cessation

⇒ Major drug interactions: MAOIs, dopaminergic drugs (CNS toxicity risk), drugs that lower seizure threshold, and drugs that affect CYP2B6, which will alter the metabolism of bupropion
⇒ The combination of naltrexone and bupropion is currently lacking renal and hepatic impairment data

**Contrave® important counseling points:**
- Excessive alcohol consumption increases the risk of seizures
- Education about signs/symptoms of suicidal thoughts and ideation
- Avoid eating with fatty meals because this increases absorption of both drugs
- Dose escalation for first 4 weeks of treatment (see package insert for details)
- Abnormally high doses of Contrave® may lead to seizures; discontinue if seizures occur
- Risk of visual problems with angle-closure glaucoma
- Common side effects include nausea, headache, dry mouth, and trouble sleeping

By Micah Miller, PharmD Candidate

Table and References on Page 5
SPIRIVA® Respimat® is a new delivery device of long-acting tiotropium bromide for COPD maintenance.² Spiriva® Respimat® contains the same ingredient in Spiriva® Handihaler®, which is the most commonly prescribed inhaler patients with COPD. The Respimat® device may be easier to use than the Handihaler® device for some patients. The Respimat® device delivers a lower dose (5 mcg) compared to the Handihaler®’s 18 mcg dose.² Smaller particles are delivered by the Respimat® into the lungs, which increases the amount of drug in the distal parts of the lungs and potentially increases systemic absorption of tiotropium. This would increase the anticholinergic effects of the medication.³

Adverse events are similar between the two devices.²,⁴ However, some studies suggest that mortality may be increased with Respimat®.⁵ These studies are controversial because the patients using Respimat® in the studies generally had more severe COPD and cardiovascular complications than patients using Handihaler®.⁵

The Tiotropium Safety and Performance in Respimat (TIOSPIR) study did not find a difference in mortality between Spiriva® Respimat® and Spiriva® Handihaler®, even in patients with an underlying arrhythmia.¹,² The patients received tiotropium via either Respimat® (n=5711) or Handihaler® (n=5694) for 3 years. Four hundred twenty-three deaths (7.4%) were observed in the Respimat® group and 439 deaths (7.7%) were observed in the Handihaler® group (HR 0.96, 95% CI 0.84 – 1.09). Lung function, based on trough FEV1, also similar between the two groups (mean difference 0.010 L, 95% CI -0.038 to 0.018 L). The time to first exacerbation almost 2 years in both groups (Respimat®, 756 days; Handihaler® 719 days; HR 0.98, 95% CI 0.93 to 1.03). Major cardiovascular events occurred in 3.9% and 3.6% in the Respimat® and Handihaler® groups, respectively. However, patients with other comorbidities were excluded so the mortality rates seen in the study may not apply to those patients.¹,²

A meta-analysis found contradictory data on the potential increase in cardiovascular and mortality risk with Respimat®.² Of 77 studies which evaluated the use of tiotropium delivered by Handihaler® or Spiriva®, 5 studies directly compared the two delivery devices. The higher plasma concentrations and increased anticholinergic effects seen with Respimat® could increase risk of death and cardiac events, but the two devices were equally effective in the studies. It is important to note that the safety data for Spiriva® Respimat® is limited, so a definitive conclusion concerning the risks is not possible.⁵

The risk of death was increased 30% with Spiriva® Respimat® compared to the Handihaler®.³ In this large (n=11,287) observational study, most of the patients were using the Handihaler® device and only 30% of patients were using the Respimat®. With the Handihaler®, the death rate was 37.5 per 1000 person-years; the death rate with Respimat® was 60.7 per 1000 person-years. The majority of deaths were from cardiovascular or cerebrovascular complications (31.6%), cancer (27.6%), and respiratory complications (19.1%). Patients with underlying cardiovascular disease had the highest risk of death with Respimat® (adjusted HR 1.36, 95% CI 1.07—1.73). The Respimat® patients had more severe COPD and were more likely to have cardiovascular disease than the patients on the Handihaler®; these differences between the groups at baseline may have confounded the results.⁵

The Respimat® device was associated with less systemic tiotropium exposure than the Handihaler® device in a pharmacokinetic study.⁶ The increased mortality risk with Respimat® is usually attributed to higher systemic absorption with Respimat®, a pharmacokinetic, crossover study found the opposite to be true. Limitations of the study include possible bias since the authors were employed by the manufacturer of Respimat® and the lack of a wash-out period between the crossover periods.⁶

Spiriva® Respimat® offers an easier to use alternative to Spiriva® Handihaler®, but should be used with caution in patients with cardiovascular disease due to a possible increase in mortality.

By Britney Bellew, PharmD Candidate

REFERENCES:

3. Mathioudakis A, Chatzimavridou-Grigoriadou V, Evangelopoulos E, Mathioudakis G, Siafakas N. Comparative mortality risk of tiotropium administered via handihaler or respimat in COPD patients: are they equivalent? Pulm Phar-
Kerydin™ (tavaborole) topical solution, 5%

Kerydin™ (tavaborole) was approved by the FDA in July 2014 to treat onychomycosis of the toenail due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*.1 Azole-resistant fungi have been discovered, so antifungal medications with a different mechanism of action are needed.2 Tavaborole inhibits fungal leucyl transfer RNA synthetase instead of lanosterol 14α-demethylase which is inhibited by azole antifungals.3 Another reason to use tavaborole instead of an oral azole is because some patients cannot take oral antifungal medications due to drug interactions.

The two newest topical antifungals are tavaborole and Jublia® (efinaconazole topical 10% solution). There are no head-to-head studies on these two drugs yet. However, tavaborole treatment produced 37% clear or mostly clear nails in studies, while efinaconazole treatment produced only 26% clear of mostly clear nails.3

The 5% solution of tavaborole was chosen for use in phase III trials based on the results of a phase II, dose-ranging study.4 Tavaborole 5% and 7.5% solutions had similar efficacy, but the 5% solution caused fewer adverse events.4

Tavaborole 5% solution use resulted in a higher cure rate compared to placebo in 526 patients with distal subungual onychomycosis.5 Patients were treated for 48 weeks and evaluated at week 52. In the tavaborole group, 10% of patients had a complete cure and 37% were almost clear of infection. Fewer than 20% of the patients in the placebo group were completely cured or almost clear of infection (1.5% cure rate; 17% almost clear). Adverse events were similar in both groups and included tinea pedis, nasopharyngitis, and upper respiratory infections. Two patients discontinued tavaborole treatment due to adverse events compared to one patient in the solution vehicle group. Limitations of this study included the vague description of success and the large number of subjects who did not complete the trial (n=78).5

**Adverse Effects**
The most common adverse reactions occurring in ≥1% of study subjects (n=791).3

- Application site exfoliation (2.7%)
- Application site erythema (1.6%)
- Application site dermatitis (1.3%)
- Application site exfoliation (2.7%)
- Application site erythema (1.6%)
- Application site dermatitis (1.3%)

**Dosing & Administration**
Tavaborole should be applied to affected toenails once a day for 48 weeks.1 Tavaborole is applied to the entire toenail(s) being treated. Tavaborole is a topical solution and is only intended for topical toenail application.1

**Conclusion**
Tavaborole is an effective topical treatment option for onychomycosis of the toenail(s).1 Tavaborole has a different mechanism of action than the other topical fungal treatments and may be the most efficacious at clearing onychomycosis of the toenail(s).

By Dawn Holt, PharmD Candidate

**REFERENCES:**

**Spiriva® Respimat® continued (from page 2)**

macol Ther 2014; 28(2):91-97.


Obstructive sleep apnea (OSA) is when breathing is paused repeatedly during sleep. The pauses usually last for 10 seconds or longer. Sleep apnea is considered obstructive when the pauses in breathing are due to the airway not being held open by the muscles in the throat.

Poor sleep may result from the pauses in breathing. Low blood oxygen levels occur due to the pauses in breathing. Untreated OSA may lead to an increase in other health problems like high blood pressure, heart disease, and problems with memory and mood.

**What causes OSA?**
Some risk factors for OSA include:
- Overweight
- 40 years old or older
- Smoking and alcohol use, especially right before bedtime
- Large tonsils or tongue
- Small mouth, throat, or jaw
- Neck size greater than 17 inches in men and 16 inches in women
- Certain ethnicities like African-Americans, Pacific Islanders, and Hispanics
- Family history of OSA

**What are the symptoms of OSA?**
- Loud snoring—usually a partner or family member notices snoring first
- Feeling tired during the day, daytime fatigue can lead to problems with your attention or make you feel irritable
- Gasping for breath during sleep
- Waking up or tossing and turning throughout the night

**What are the treatment options for OSA?**
- **Continuous Positive Airway Pressure Device (CPAP)**
  - This device is a mask that connects to a machine that sits next to your bed.
  - You wear the mask while you sleep to help keep your airway open.
  - The mask fits over your nose, and there are different options for the mask design.
- **Dental Devices**
  - These go in your mouth to move your jaw forward and help keep your airway open throughout the night while you sleep.
- **Surgery**
  - This is a last resort if other options do not work or if you have very severe symptoms.

**Tips for using CPAP**
1) If the CPAP is noisy or irritating, have the mask checked to see if it fits correctly. You can also try a different type of mask.
2) If you have a dry nose from the CPAP mask, you can use a nasal saline spray right before bedtime and the next morning.
3) Limit fluids right before bedtime so you do not have to get up in the middle of the night and then have to put your CPAP mask back on.

By Sydney Schrammeck, PharmD Candidate

**REFERENCES:**


2. Schmidt-Nowara W. Sleep apnea in adults. In: UpToDate, Collop N (Ed), UpToDate, Waltham, MA. (Accessed October 27, 2014)


### Obesity Agents References (from page 1)


### Comparison of Contrave® and Qsymia®

<table>
<thead>
<tr>
<th>Contrave® (naltrexone/bupropion)</th>
<th>Qsymia® (phentermine/topiramate ER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination of an antidepressant (bupropion) and opioid receptor antagonist (naltrexone)</td>
<td>Combination of sympathomimetic stimulant (phentermine) and antiepileptic agent (topiramate)</td>
</tr>
<tr>
<td>One tablet strength (naltrexone 8 mg/bupropion 90 mg) with one recommended maintenance dose (2 tablets twice daily)</td>
<td>Multiple strengths available with two recommended doses: normal maintenance dose (phentermine 7.5 mg/topiramate ER 46 mg) and high dose (phentermine 15 mg/topiramate ER 92 mg)</td>
</tr>
<tr>
<td>Twice daily dosing (morning and evening)</td>
<td>Once daily dosing (morning)</td>
</tr>
<tr>
<td>4-week escalation schedule to reach recommended maintenance dose (see package insert for details)</td>
<td>2-week escalation schedule to reach normal maintenance dose, and another 2-week escalation to reach high dose (see package insert for details)</td>
</tr>
<tr>
<td>5% weight loss with minimal dietary/exercise intervention, but 9.3% weight loss with intense dietary/exercise intervention</td>
<td>8.6% weight loss on high dose, but minimal dietary/exercise intervention</td>
</tr>
<tr>
<td>Pregnancy category X because weight loss during pregnancy offers no maternal benefit and possible fetal risk</td>
<td>Pregnancy category X because of risk of fetal birth defects</td>
</tr>
<tr>
<td>No current restriction for purchase (available at any pharmacy)</td>
<td>REMS program which restricts sale to certified pharmacies; pregnancy testing required before and during Qsymia® use</td>
</tr>
<tr>
<td>Use of high amounts of alcohol increase risk of seizures</td>
<td>Use of any amount of alcohol increases risk of CNS depression and should be avoided</td>
</tr>
<tr>
<td>Seizure risk is most associated with overdose—not abrupt discontinuation of Contrave</td>
<td>Seizure risk is most associated with abrupt discontinuation—not overdose of Qsymia</td>
</tr>
</tbody>
</table>
PATIENT INFORMATION: Hypothyroidism: How Is Your Thyroid?

Hypothyroidism is a condition where your thyroid gland does not make enough thyroid hormones. Thyroid hormones are essential for proper functioning of every organ in your body. Thyroid hormones (T3 and T4) help your body extract energy from food, control body temperature, and control blood pressure.

Symptoms of Hypothyroidism:
- Fatigue
- Dry skin or brittle nails
- Cold intolerance
- Unexplained weight gain
- Constipation
- Thinning hair
- Irregular periods

Possible Causes of Hypothyroidism:
- Autoimmune disease
- Thyroid surgery
- Radiation exposure
- Certain medications like lithium and amiodarone

Most Common Risk Factors:
- Female
- Over 60 years old
- Pregnancy
- Known autoimmune disorder (diabetes, rheumatoid arthritis, etc)

Complications:
- Goiter (swollen thyroid)
- Peripheral neuropathy (pain in extremities)
- Infertility
- Birth defects

Diagnosing Hypothyroidism:
Your doctor will order a blood test if necessary. The blood test measures TSH (thyroid stimulating hormone) and thyroxine (T4). High TSH often means you have hypothyroidism.

Treatment:
Your doctor will prescribe a thyroid replacement medication for you. There are synthetic and natural, desiccated thyroid medications available. Synthetic drugs contain T4 while natural drugs contain T3 and T4. Once you begin taking medication, you will likely feel better in 1-4 weeks. You will need to continue thyroid replacement for the rest of your life. The most common thyroid medications are:
- Synthroid® (T4)
- Levothyroxine (T4)
- Armour Thyroid® (T3 & T4)
- Nature-Thyroid® (T3 & T4)

Tips for Taking Thyroid Medications:
- Stay with the same brand of thyroid medication. Do not change generic manufacturers.
- Take your thyroid medication every day, even after you feel better.
- Take your thyroid medication at same time every day (preferably first thing in morning, 30-60 minutes before eating).
- Do not drink or eat soy-containing products within 4 hours of taking thyroid medication.
- Do not take products containing calcium, iron, or aluminum hydroxide within 4 hours of taking thyroid medication.
- Keep track of missed pills
- Watch out for signs of too much thyroid such as insomnia, racing heart, shakiness, muscle weakness, high body temperature, and shortness of breath.

Once You Start Taking Medication:
Your doctor will order blood tests when needed. It may take a few months to find the dose that is right for you. Notify your doctor if you start any new medication because you may need to adjust your thyroid dose.

By Dawn Holt, PharmD Candidate

REFERENCE: