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The University at Buffalo School of Pharmacy and Pharmaceutical Sciences (UB SPPS) Drug Information Newsletter is dedicated to providing timely information relevant to healthcare practitioners in New York. The newsletter supplies information on clinical practice guidelines, medication safety issues, new drug approvals/medications under development, medication shortages, and drug class reviews.

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*Ryan Lindenau, PharmD*

**Introduction**

Nearly 50% of patients with type 2 diabetes mellitus fail to meet their glycemic goals despite advances in therapy due to barriers including non-adherence, failure of prescribers to titrate and adjust treatment, and limitations in the healthcare system.\(^1\) Implementation of newer therapies in combination with comprehensive care plans and patient education may address some of these barriers.

There are several treatment options for patients with type 2 diabetes mellitus, including biguanides (i.e., metformin), sulfonylureas, glucagon-like peptide-1 (GLP-1) receptor agonists (RAs), dipeptidyl peptidase-4 (DPP-4) inhibitors, alpha-glucosidase (AG) inhibitors, thiazolidinediones, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and insulin. Current treatment guidelines support lifestyle modification and metformin as
first-line therapy; alternative agents or dual or triple therapy may be considered depending on patient-specific factors, e.g., baseline glycosylated hemoglobin (A1c) and renal function.\textsuperscript{2,3} The American Association of Clinical Endocrinologists (AACE) recommends GLP-1 RAs as first-line pharmacologic options in patients with a contraindication or intolerance to metformin therapy; AACE also recommends GLP-1 RAs in combination therapy.\textsuperscript{2}

GLP-1 RAs activate the GLP-1 receptor to increase glucose-dependent insulin secretion, decrease glucose-dependent glucagon secretion, slow gastric emptying, and increase satiety. Currently available GLP-1 RAs include exenatide, liraglutide, albiglutide, and dulaglutide.\textsuperscript{4} The Food and Drug Administration (FDA) approved albiglutide (Tanzem\textsuperscript{TM}; GlaxoSmithKline) in April 2014 for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. Albiglutide is a once-weekly injectable agent; though approved for treatment of type 2 diabetes, it has not been studied for type 1 diabetes. Albiglutide is a novel compound comprised of a DPP-4-resistant GLP-1 dimer fused to human albumin, extending its half-life and allowing for less frequent, weekly dosing.\textsuperscript{5,6}

\textit{Efficacy

FDA approval of albiglutide was based on 8 phase III trials (HARMONY series) involving over 2,000 diabetes patients who were previously uncontrolled with various oral antihyperglycemic agents, insulin, and/or diet and exercise.\textsuperscript{7} These trials are outlined in Table 1.\textsuperscript{8-15} Albiglutide was studied as monotherapy and in combination with metformin, metformin with a sulfonylurea, a thiazolidinedione (with and without metformin), and insulin glargine (with and without other oral antidiabetic agents). Comparators included placebo, glimepiride, pioglitazone, liraglutide, sitagliptin, insulin lispro, and insulin glargine. Trial durations ranged from 26 to 156 weeks. With the exception of Harmony 5, the primary efficacy endpoint for all studies was change from baseline to study completion in A1c.

Overall, patients in these studies had a mean baseline A1c of approximately 8%.\textsuperscript{8-15} Whether administered as monotherapy or in combination with other antidiabetic drugs, use of albiglutide resulted in a mean reduction in A1c of approximately 1% (range: 0.55 to 0.9). Compared to placebo, as monotherapy and added on to pioglitazone ± metformin, as well as sitagliptin and glimepiride when added on to metformin, statistically significant differences were observed favoring albiglutide.\textsuperscript{8-10} Albiglutide was also determined to be non-inferior to insulin glargine, when administered in combination with metformin ± sulfonylurea, and insulin lispro, when administered in combination with insulin glargine.\textsuperscript{11,13} However, when compared to liraglutide, albiglutide failed to meet non-inferiority criteria, and it was associated with less A1c reduction compared to pioglitazone, in combination with metformin and glimepiride.\textsuperscript{12,14} Notably, albiglutide use was assessed in patients with renal impairment and compared to dose-adjusted sitagliptin, in a 26-week, randomized, double-blind study.\textsuperscript{15} Significant reductions in A1c favoring albiglutide were observed, without regard to degree of renal impairment (estimated glomerular filtration rate [eGFR] 15 to 89 mL/min/1.73 m\textsuperscript{2}).

In addition to A1c, weight was evaluated in all of the outlined studies. Overall, modest weight-loss was observed in patients using albiglutide (range: 0.4 to 1.2 kg).\textsuperscript{8-15} In 1 study, weight gain of 0.28 kg was reported.\textsuperscript{9} When compared to other oral antidiabetic drugs, most of the differences were not statistically significant.\textsuperscript{9,10} Significant differences were observed between albiglutide and insulin glargine, with insulin glargine eliciting weight gain.\textsuperscript{13} Significant differences were also observed between albiglutide and liraglutide, with greater weight-loss observed in patients using liraglutide.\textsuperscript{14}
Safety

Boxed warnings

Albiglutide carries a boxed warning for acute pancreatitis and medullary thyroid carcinoma (MTC). Acute pancreatitis, a rare but serious adverse reaction that has been associated with other GLP-1 RAs, occurred in trials among albiglutide users although a causal relationship has not been established. Emerging large observational data sets have found no statistically significant increased rates of pancreatic disease with usage of GLP-1 RAs. Thyroid C-cell tumors have been observed in animal studies following administration of albiglutide at clinically relevant levels. It is unknown whether these tumors, including MTC, may develop in humans receiving albiglutide.

To address these concerns, the FDA requires a Risk Evaluation and Mitigation Strategy (REMS), which includes a letter to the healthcare provider and medication guide to be dispensed to patients receiving albiglutide, informing all of the potential risk for MTC and acute pancreatitis.

Adverse reactions

In phase III trials, adverse reactions reported more frequently with albiglutide compared to placebo included hypoglycemia, infection (upper respiratory, influenza, sinusitis), cough, back pain, injection-site reactions, and elevation in liver enzymes. Gastrointestinal (GI) adverse effects have been commonly reported with albiglutide, as with other GLP-1 RAs; these side effects may occur more frequently in patients with renal dysfunction. Thus, the manufacturer recommends monitoring renal function in those with renal impairment reporting severe GI reactions. Notably, compared to liraglutide, participants receiving albiglutide experienced fewer GI adverse effects (39.5% vs. 49%, p=0.00013) although injection-site reactions were higher in the albiglutide group (12.9 vs. 5.4%, p=0.0002). Atrial fibrillation/flutter occurred more frequently among albiglutide users, most commonly among male participants with cardiac or renal disease. There are no recommendations regarding use of albiglutide in these patients.

When initiating albiglutide in combination with a sulfonylurea or insulin, dose reduction of the sulfonylurea or insulin may be warranted to reduce the risk of hypoglycemia. The HARMONY trials showed a 16% incidence of hypoglycemia in combination with insulin glargine and a 13% incidence in those taking a sulfonylurea compared to a 2% incidence of hypoglycemia with albiglutide monotherapy.

Drug interactions

In studies, albiglutide has not demonstrated a clinically relevant effect on the absorption of several orally administered medications, including warfarin, digoxin, and oral contraceptives. When administered concurrently with simvastatin, the maximum plasma concentration of simvastatin increased from 18 to 98%; however, the clinical significance of this effect has not been established. Of note, albiglutide may delay gastric emptying; this may impact the absorption of concomitantly administered oral medications.
### Table 1. Summary of albiglutide clinical trials.

<table>
<thead>
<tr>
<th>HARMONY trial</th>
<th>Duration</th>
<th>Design</th>
<th>Interventions</th>
<th>Population</th>
<th>Mean change from baseline A1c</th>
<th>Mean change from baseline weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Study 2<sup>8</sup> | 52 weeks | R, DB  | Albiglutide 30 mg SC once weekly  
Albiglutide 50 mg SC once weekly  
Placebo  
*Add-on to pioglitazone ± metformin | n=296 patients inadequately controlled on diet or exercise  
Baseline A1c (mean): 8.1% | Albiglutide 30 mg: -0.7  
• Difference from placebo: -0.8, 95% CI -1.1 to -0.6  
Albiglutide 50 mg: -0.9  
• Difference from placebo: -1.0, 95% CI -1.3 to -0.8  
Placebo: +0.2 | Albiglutide: -0.4 to -0.9 kg  
Placebo: -0.7 kg  
• Difference and p-values not reported |
| **Add-on therapy** |          |        |               |            |                               |                                  |
| Study 1<sup>9</sup> | 52 weeks | R, DB  | Albiglutide 30 mg SC once weekly  
Placebo  
*Add-on to pioglitazone ± metformin | n=301 patients inadequately controlled on pioglitazone ± metformin  
Baseline A1c (mean): 8.1% | Albiglutide: -0.8  
• Difference from placebo: -0.8, 95% CI -1.0 to -0.6  
Placebo: -0.1 | Albiglutide: +0.28 kg  
Placebo: +0.45 kg  
• Difference: -0.2 kg, p=0.72 |
| Study 3<sup>10</sup> | 104 weeks | R, DB  | Albiglutide 30 to 50 mg SC once weekly  
Sitagliptin 100 mg PO daily  
Glimepiride 2 to 4 mg PO daily  
Placebo  
*Add-on to metformin | n=999 patients inadequately controlled on metformin  
Baseline A1c (mean): 8.1% | Albiglutide: -0.6  
• Difference from placebo: -0.9, 95% CI -1.16 to -0.65  
• Difference from sitagliptin: -0.4, 95% CI -0.53 to -0.17  
• Difference from glimepiride: -0.3, 95% CI -0.45 to -0.09  
• Difference from glimepiride: -0.4  
Placebo: +0.3 | Albiglutide: -1.21 kg  
• Difference from placebo: -0.2 kg, 95% CI -1.1 to 0.7  
• Difference from sitagliptin: -0.4 kg, 95% CI -1.0 to 0.3  
• Difference from glimepiride: -2.4 kg, 95% CI -3.0 to -1.7  
Sitagliptin: -0.86 kg  
Glimepiride: +1.17 kg  
Placebo: -1.00 kg |
| Study 4<sup>11</sup> | 52 weeks | R, OL, non-inferiority | Albiglutide 30 mg SC once weekly  
Insulin glargine 10 units SC daily  
*Add-on to metformin ± sulfonylurea | n=779 patients inadequately controlled on metformin ± sulfonylurea  
Baseline A1c (mean): 8.28 to 8.36% | Albiglutide: -0.67  
Insulin glargine: -0.79  
• Treatment difference: 0.11, 95% CI 0.04 to 0.27  
• Met non-inferiority margin | Albiglutide: -1.06 kg  
Insulin glargine: +1.57 kg  
• Difference: -2.61 kg, 95% CI: -3.20 to -2.02 |

*OL = open-label, DB = double-blind, SC = subcutaneous, PO = oral*
<table>
<thead>
<tr>
<th>HARMONY trial</th>
<th>Duration</th>
<th>Design</th>
<th>Interventions</th>
<th>Population</th>
<th>Mean change from baseline A1c</th>
<th>Mean change from baseline weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 5</strong>$^{12}$</td>
<td>156 weeks; primary endpoint at week 52</td>
<td>R, DB</td>
<td>Albiglutide 30 mg SC once weekly&lt;br&gt;Pioglitazone 30 mg PO daily&lt;br&gt;Placebo&lt;br&gt;*Add-on to metformin and glimepiride</td>
<td>n=685 patients inadequately controlled on metformin and glimepiride&lt;br&gt;Baseline A1c (mean): 8.24%</td>
<td><strong>Albiglutide: -0.55</strong>&lt;br&gt;• Difference from placebo: -0.87, 95% CI -1.07 to -0.68&lt;br&gt;• Difference from pioglitazone: +0.25, 95% CI -0.53 to -0.17&lt;br&gt;Pioglitazone: -0.80&lt;br&gt;Placebo: +0.33</td>
<td>Albiglutide: -0.42 kg&lt;br&gt;Pioglitazone: +4.4 kg&lt;br&gt;Placebo: -0.40 kg&lt;br&gt;• Differences and p-values not reported</td>
</tr>
<tr>
<td><strong>Study 6</strong>$^{13}$</td>
<td>26 weeks</td>
<td>R, OL, non-inferiority</td>
<td>Albiglutide 30 to 50 mg SC once weekly&lt;br&gt;Insulin lispro, titrated to effect, TID with meals&lt;br&gt;*Add-on to insulin glargine</td>
<td>n=563 patients inadequately controlled on insulin glargine&lt;br&gt;Baseline A1c (mean): 8.4 to 8.5%</td>
<td><strong>Albiglutide: -0.82</strong>&lt;br&gt;Insulin lispro: -0.66&lt;br&gt;• Treatment difference: -0.16, 95% CI -0.32 to 0.00&lt;br&gt;• Met non-inferiority margin</td>
<td>Albiglutide: -0.73 kg&lt;br&gt;Insulin lispro: +0.81 kg&lt;br&gt;• Difference and p-values not reported</td>
</tr>
<tr>
<td><strong>Study 7</strong>$^{14}$</td>
<td>32 weeks</td>
<td>R, OL, non-inferiority</td>
<td>Albiglutide 30 to 50 mg SC once weekly&lt;br&gt;Liraglutide 0.6 to 1.8 mg SC daily&lt;br&gt;*Add-on to OADs</td>
<td>n=422 patients inadequately controlled on metformin, a TZD, sulfonylurea, or combination (OADs)&lt;br&gt;Baseline A1c (mean): 8.2%</td>
<td><strong>Albiglutide: -0.8</strong>&lt;br&gt;Liraglutide: -1.0&lt;br&gt;• Treatment difference: +0.2, 95% CI 0.08 to 0.34&lt;br&gt;• Did not meet non-inferiority margin</td>
<td>Albiglutide: -0.6 kg&lt;br&gt;Liraglutide: -2.2 kg&lt;br&gt;• Difference: +1.6 kg, 95% CI 1.1 to 2.1</td>
</tr>
<tr>
<td><strong>Study 8</strong>$^{15}$</td>
<td>26 weeks</td>
<td>R, DB</td>
<td>Albiglutide 30 to 50 mg SC once weekly&lt;br&gt;Sitagliptin 25-100 mg PO daily, dose dependent on renal function</td>
<td>n=486 patients with renal impairment, inadequately controlled on diet and exercise, ± metformin, TZD, sulfonylurea&lt;br&gt;Baseline A1c (mean): 8.1 to 8.2%&lt;br&gt;Renal impairment:&lt;br&gt;• mild: n=250&lt;br&gt;• moderate: n=200&lt;br&gt;• severe: n=36</td>
<td><strong>Albiglutide: -0.8</strong>&lt;br&gt;Sitagliptin: -0.5&lt;br&gt;• Treatment difference: -0.3, 95% CI -0.49 to -0.15</td>
<td>Albiglutide: -0.8 kg&lt;br&gt;Sitagliptin: -0.2 kg&lt;br&gt;• Difference: -0.6 kg, 95% CI -1.1 to -0.1</td>
</tr>
</tbody>
</table>

R=randomized, DB=double-blind, SC=subcutaneously, A1c=glycosylated hemoglobin, CI=confidence interval, PO=by mouth, OL=open-label, TID=3 times daily, TZD=thiazolidinedione, OADs=oral antidiabetic drugs
Dosage and Administration

The recommended starting dose of albiglutide is 30 mg once weekly, delivered by subcutaneous injection into the abdomen, thigh, or upper arm. The dosage may be increased to 50 mg as needed for improved glycemic control. Albiglutide is administered without regard to meals but should be administered on the same day each week. If a dose is missed, patients should be instructed to administer the missed dose as soon as possible, within 3 days, and resume dosing on the usual day of administration. If more than 3 days has elapsed, the patient should skip the dose and wait until his/her next scheduled dose. No dose adjustment is necessary for renal impairment (eGFR 15 to 89 mL/min/1.73 m²).

Storage and Handling

Albiglutide is supplied as a single-dose pen containing lyophilized powder that must be reconstituted prior to administration. Patients should be counseled on the reconstitution process prior to dispensing as the process requires multiple steps and should be completed at least 15 to 30 minutes prior to administration. The reconstituted solution is stable for 8 hours and must be used within this time frame. Pens should be stored in the refrigerator at 36-46ºF and should not be frozen. Unopened pens can be stored at room temperature (below 86ºF) for 28 days. The pens should be disposed in a sharps container or similar heavy-duty plastic household container.

Place in Therapy

Based on the recommendations of the American Diabetes Association and AACE, GLP-1 RAs may be appropriate as an alternative to metformin monotherapy or as an additional agent in a dual or triple combination. However, per the manufacturer recommendations, albiglutide should not be used as first-line therapy, due to the risks for MTC and acute pancreatitis.

In clinical trials, A1c reductions of approximately 1% were observed in patients receiving albiglutide; this reduction is similar to those of other agents in the GLP-1 RA class (see Table 2). When compared to liraglutide, however, albiglutide failed to meet non-inferiority criteria. In addition to less glucose-lowering, albiglutide use was associated with less weight-loss. Still, there were fewer reports of nausea and vomiting with albiglutide compared to liraglutide. Comparative use of albiglutide and other GLP-1 RAs (namely, exenatide extended-release and dulaglutide) has not been evaluated.

Albiglutide does not require renal dose adjustment, unlike exenatide extended-release, which is not recommended in patients with creatinine clearance (CrCl) <30 mL/min. Unlike other GLP-1 RAs, its use in renal impairment has been evaluated in a clinical efficacy study. The composition of albiglutide is also unique: albiglutide is comprised of 2 copies of a GLP-1 dimer fused to human albumin, leading to increased size (molecular weight 72.97 kDa). It is postulated that albiglutide follows a metabolic pathway similar to native human serum albumin, which is catabolized primarily by the vascular endothelium. Due to its composition and size, penetration of the central nervous system may be lower compared to other GLP-1 RAs, potentially resulting in fewer GI adverse effects (i.e., nausea and vomiting).

Albiglutide’s cumbersome reconstitution procedure is a limitation, especially in consideration of the injection solutions which do not require manipulation. Dulaglutide, for example, does not require reconstitution and
is supplied as a single-use pen with a hidden needle.\textsuperscript{20} Patients using dulaglutide have reported ease of administration, little pain, and decreased fear of injection.\textsuperscript{24}

### Table 2. Characteristics of selected GLP-1 RAs\textsuperscript{18-23}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
<th>Exenatide extended-release</th>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Tanzeum\textsuperscript{TM}</td>
<td>Trulicity\textsuperscript{TM}</td>
<td>Bydureon\textsuperscript{®}</td>
<td>Victoza\textsuperscript{®}</td>
</tr>
<tr>
<td>FDA approval</td>
<td>April 2014</td>
<td>September 2014</td>
<td>January 2012</td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM</td>
<td></td>
<td></td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Obesity (Saxenda\textsuperscript{®})</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Single-dose pen</td>
<td>Single-dose pen and prefilled syringe</td>
<td>Single-dose pen and tray/vial</td>
<td>Multi-dose pen</td>
</tr>
<tr>
<td></td>
<td>• Requires reconstitution</td>
<td>• No reconstitution</td>
<td>• Requires reconstitution</td>
<td>• No reconstitution</td>
</tr>
<tr>
<td></td>
<td>• 15 minutes prior for 30 mg dose, 30 minutes prior for 50 mg dose</td>
<td>• Supplied with 29 G needle</td>
<td>• Immediately prior to administration</td>
<td>• Needles not supplied</td>
</tr>
<tr>
<td></td>
<td>• Supplied with 29 G needle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>30 mg SC once weekly; titrate to 50 mg weekly as needed</td>
<td>0.75 mg SC once weekly; titrate to 1.5 mg weekly as needed</td>
<td>2 mg SC once weekly</td>
<td>0.6 mg SC daily for 1 week, then 1.2 mg daily thereafter; titrate to 1.8 mg daily as needed</td>
</tr>
<tr>
<td>Potential A1c reduction</td>
<td>~1%</td>
<td>~1.5%</td>
<td>~1.5%</td>
<td>~1.5%</td>
</tr>
<tr>
<td>Potential weight-loss\textsuperscript{a}</td>
<td>1.2 kg</td>
<td>3.1 kg</td>
<td>2.3 kg</td>
<td>2.8 kg</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Personal or family history of MTC or MEN-2; hypersensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boxed warnings</td>
<td>MTC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common ADRs</td>
<td>Nausea, vomiting, diarrhea, injection site reactions/rash, dyspepsia</td>
<td>Nausea, vomiting, diarrhea, abdominal pain, decreased appetite, dyspepsia</td>
<td>Nausea, vomiting, diarrhea, headache, constipation, injection site reactions/rash, dyspepsia</td>
<td>Nausea, vomiting, diarrhea, headache, anti-liraglutide antibody formation, injection site reactions/rash, dyspepsia</td>
</tr>
<tr>
<td>Dose adjustment in renal impairment</td>
<td>Not needed, eGFR $\geq$15 mL/min/1.73 m\textsuperscript{2}</td>
<td>Not needed, including ESRD</td>
<td>Drug should not be used if CrCl &lt;30 mL/min</td>
<td>Not recommended, but use with caution</td>
</tr>
<tr>
<td>Pregnancy risk</td>
<td>Category C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per month</td>
<td>$\sim$325</td>
<td>$\sim$490</td>
<td>$\sim$450</td>
<td>$\sim$450</td>
</tr>
</tbody>
</table>

FDA=Food and Drug Administration, T2DM= type 2 diabetes mellitus, SC=subcutaneously, MTC= medullary thyroid carcinoma, MEN 2= Multiple Endocrine Neoplasia syndrome type 2, eGFR=estimated glomerular filtration rate, ESRD=end-stage renal disease, CrCl=creatinine clearance

\textsuperscript{a}Observed in 52-week studies for albiglutide and dulaglutide, 26-week study for liraglutide, and 24-week study for exenatide extended-release

### Conclusion

Albiglutide is a new GLP-1 RA approved for the treatment of type 2 diabetes. Potential advantages of albiglutide include its cost (compared to other GLP-1 RAs), once-weekly dosing, fewer GI side effects, and safety in renal impairment. Its limitations include less A1c reduction potential, potentially minimal weight-loss, and increased risk of pancreatitis and thyroid C-cell tumors. Additionally, albiglutide is only available as a

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parenteral agent, and administration requires careful reconstitution. At this time, there are no published studies directly comparing all of the GLP-1 RAs. Selection of an agent should be individualized and based on a thorough evaluation of patient and disease characteristics, as well as patient preferences, and treatment goals.

References

Contrave®, a combination extended-release product containing bupropion and naltrexone, was approved by the United States (US) Food and Drug Administration (FDA) on September 10, 2014.¹² Contrave® joins a handful of other FDA-approved prescription drugs for weight management; however, it is unique in its combined mechanisms of action. Separately, bupropion is an aminoketone antidepressant, and naltrexone, an opioid antagonist. Combined, their effects leading to weight-loss are not fully understood. Data suggest that the combination product impacts food intake and weight management by modulating 2 distinct pathways—the hypothalamic pathway, involving pro-opiomelanocortin (POMC) neurons, and the mesolimbic pathway, involving dopamine. Stimulation of POMC neurons in the hypothalamus is thought to result in induced satiety, inhibited food intake, and increased resting energy expenditure. Bupropion is thought to stimulate these POMC neurons while naltrexone blocks opioid-mediated POMC autoinhibition. Bupropion and naltrexone are both theorized to impact mesolimbic dopamine reward systems related to food intake.³⁴

According to a 2013 report by the US Department of Health and Human Services, more than one-third of adults (34.9%) were obese in 2011 – 2012.⁵ Based on current trends, investigators have projected a prevalence of 51% by 2030.⁶ Annual medical costs of obesity have been estimated at $147 billion, per a 2009 study analyzing expenditure in the US in 2008.⁷ As the cost, prevalence, and morbidity/mortality associated with obesity grow, so does the demand for more effective treatment options. With dozens of prescription agents and combination products currently in development, it is increasingly important to critically evaluate these products and determine their appropriate role in obesity management. Notably, there is a lack of consensus regarding optimal pharmacologic therapy for obese and overweight patients. The available clinical treatment guidelines for the management of obesity from the American Heart Association, American College of Cardiology, and Obesity Society include a disclaimer that pharmacotherapy was not a focus of their review.⁸ The guidelines simply mention pharmacotherapy as an optional adjunct to behavioral modifications in select patients, but there are no specific recommendations on available agents.
Contrave® is indicated for chronic weight management as an adjunct to modified diet and exercise in adult patients with (1) body mass index (BMI) ≥30 kg/m² or (2) BMI ≥27 kg/m² with ≥1 weight-related comorbidity (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus). This product is not approved for treatment of depression or opioid/alcohol dependence. Contrave® is available as an extended-release tablet containing 8 mg of naltrexone and 90 mg of bupropion hydrochloride. The manufacturer recommends a 3-week dose titration as seen in Table 1. The current average wholesale price for 120 Contrave® tablets (30-day supply) is $239.40.

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Morning</td>
</tr>
<tr>
<td>Week 1</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Week 2</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Week 3</td>
<td>2 tablets</td>
</tr>
<tr>
<td>Week 4 and thereafter</td>
<td>2 tablets</td>
</tr>
</tbody>
</table>

Table 1: Recommended Contrave® dose titration.

Clinical Efficacy

The efficacy and safety of Contrave® were evaluated in 4 phase III trials (COR-I, COR-BMOD, COR-II, and COR-Diabetes), outlined in Table 2. COR-I, COR-BMOD, and COR-II included obese or overweight patients with either hypertension or dyslipidemia. Patients with diabetes, uncontrolled hypertension or hyperlipidemia, significant chronic disease (cardiovascular, renal, hepatic, etc.), serious psychiatric illness, or history of seizures or drug/alcohol abuse were excluded. In contrast, COR-Diabetes included overweight patients with type 2 diabetes, with or without hypertension and/or dyslipidemia. Exclusion criteria for COR-Diabetes were type 1 diabetes, severe diabetic micro- or macrovascular complications, significant chronic disease, serious psychiatric illness, or history of seizures or drug/alcohol abuse. Pregnant patients and those with obesity of known endocrine origin were also excluded from all 4 studies.

The phase III studies were multi-center, double-blind trials in which patients were randomized to receive Contrave® or placebo for up to 56 weeks. Subjects in COR-I, COR-II, and COR-Diabetes were encouraged to follow a hypocaloric diet and increase physical activity, through counseling and written instruction. Subjects in COR-BMOD underwent intensive behavioral modification involving a total of 28 group meetings with registered dietitians, behavioral psychologists, or exercise specialists. Co-primary endpoints for all phase III studies were percent change in weight from baseline and proportion of patients with ≥5% weight-loss.

Overall, 4,536 patients were evaluated; at baseline, 24% had hypertension, 54% had dyslipidemia, and 10% had type 2 diabetes. Across the 4 trials, the mean age was 46 years, and 83% of patients were female. The majority (77%) of patients were Caucasian; 18% were Black, and 5% were of other races. The mean BMI was 36 kg/m². In all 4 studies, use of Contrave® was associated with significantly greater weight-loss compared to placebo. Also, the proportion of patients achieving ≥5% weight-loss was significantly greater with Contrave® vs. placebo.
Table 2. Summary of efficacy and safety outcomes in phase III Contrave® studies.4,10-12

<table>
<thead>
<tr>
<th>Study and objective</th>
<th>Design</th>
<th>Enrollment</th>
<th>Treatment arms</th>
<th>Mean % change in weight, difference from placebo</th>
<th>% subjects with ≥5% weight-loss</th>
</tr>
</thead>
</table>
| COR-I Greenway et al, 2010 | - R, DB, PC  
- Multicenter  
- 56-week | - n=1742 patients  
- Age 18-65 years  
- BMI 30-45 kg/m² or BMI 27-45 kg/m² with controlled HTN and/or HLD | 1. NB 16-360 mg/day  
2. NB 32-360 mg/day  
3. Placebo | 1. -5.0%  
2. -6.1%  
3. -1.3%, N/A | 1. 39%*  
2. 48%*  
3. 16% |
| COR-BMOD Wadden et al, 2011 | - R, DB, PC  
- Multicenter  
- 56-week | - n=793 patients  
- Age 18-65 years  
- BMI 30-45 kg/m² or BMI 27-45 kg/m² with controlled HTN and/or HLD | 1. NB 32-360 mg/day + BMOD  
2. Placebo + BMOD | 1. 9.3%  
2. 5.1%, N/A | 1. 66.4%*  
2. 42.5% |
| COR-II Apovian et al, 2013 | - R, DB, PC  
- Multicenter  
- 56-week  
- 28-week + 28-week extension | - n=1496 patients  
- Age 18-65 years  
- BMI 30-45 kg/m² or BMI 27-45 kg/m² with controlled HTN and/or HLD | 1. NB 32-360 mg/day  
2. Placebo | 1. -6.5% at 28 weeks  
Difference -4.6%*  
-6.4% at 56 weeks  
Difference -5.2%*  
2. -1.9% at 28 weeks, N/A  
-1.2% at 56 weeks, N/A | 1. 68.8%* (per protocol)  
2. 22.3% |
| COR-Diabetes Hollander et al, 2013 | - R, DB, PC  
- Multicenter  
- 56-week | - n=505 patients  
- Age 18-70 years  
- BMI 27-45 kg/m²  
- HbA1c 7-10%, FBG <270 mg/dL  
- Type 2 diabetes, without OAD or on stable dose for ≥3 months | 1. NB 32-360 mg/day  
2. Placebo | 1. -5.0%  
2. -1.8%, N/A | 1. 44.5%*  
2. 18.9% |

R=randomized, DB=double blind, PC=placebo controlled, BMI=body mass index, HTN=hypertension, HLD=hyperlipidemia, NB=naltrexone-bupropion combination therapy, N/A=not applicable, BMOD=intensive behavior modification, HbA1c=glycosylated hemoglobin, FBG=fasting blood glucose, OAD=oral antidiabetic drug
*p<0.001 vs. placebo
Despite the positive findings in these trials, there are several limitations to note. Patients met specified BMI criteria, but they were otherwise without significant health issues. Though COR-I, COR-II, and COR BMOD allowed for comorbidities of hypertension and dyslipidemia, patients with diabetes and active cardiovascular disease were excluded.\textsuperscript{4,10,11} In COR-Diabetes, patients with type 2 diabetes on insulin or glucagon-like peptide-1 receptor agonists were excluded.\textsuperscript{12} Across the 4 trials, the majority of participants were female and Caucasian, further limiting the external validity of these studies.\textsuperscript{4,10-12} Also, there was a high attrition rate. Approximately half of participants (49.9\%) completed COR-I. Comparatively, 54\% completed COR II, approximately 58\% completed COR-BMOD, and approximately 56\% completed COR-Diabetes. Of note, discontinuation typically occurred within the first 8 weeks. The most common reasons for study discontinuation were adverse events (treatment groups) or insufficient weight-loss (placebo groups).

\textbf{Safety}

Contrave\textsuperscript{®} carries a boxed warning for increased risk of suicidal thoughts in pediatric and young adult patients taking antidepressants.\textsuperscript{1} Contraindications include uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, pregnancy, chronic opioid use, patients using other bupropion-containing products, patients who have used monoamine oxidase inhibitors within 14 days, and patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs.

In phase III trials, groups treated with Contrave\textsuperscript{®} consistently reported more adverse effects and had higher treatment discontinuation rates, compared to placebo, attributed to adverse effects.\textsuperscript{4,10-12} The most common adverse effect reported with Contrave\textsuperscript{®} was transient nausea, which was most prevalent during dose titration. Additional adverse effects with combination therapy included headache, constipation, dizziness, and insomnia. Serious adverse events were reported infrequently; those determined to be potentially treatment-related included atrial fibrillation (n=2),\textsuperscript{10} cholecystitis (n=2),\textsuperscript{11} myocardial infarction (n=1),\textsuperscript{12} and seizures (n=1, without a history of seizures). In COR-I, researchers observed a transient increase in systolic and diastolic blood pressure of about 1.5 mmHg in patients treated with Contrave\textsuperscript{®}.\textsuperscript{4}

The FDA recommends monitoring heart rate and blood pressure prior to and during Contrave\textsuperscript{®} treatment.\textsuperscript{1,2} Blood glucose should be monitored closely in patients taking antidiabetic medications due to the potential for weight-loss to cause hypoglycemia.\textsuperscript{1}

\textbf{Discussion}

Pharmacists and other healthcare providers must rely on available literature and clinical judgment in making recommendations on prescription weight management agents. Published trials demonstrate significantly greater weight-loss (with or without intensive behavioral modification) in patients using Contrave\textsuperscript{®} compared to placebo.\textsuperscript{4,10-12} However, the trials excluded patients with significant, uncontrolled chronic diseases, psychiatric illnesses, and other conditions, as well as concurrent use of drugs and dietary supplements with known psychotropic or anorectic effects, limiting the external validity of their findings. Additionally, clinical experience with the drug is lacking, and potential adverse effects and safety issues—mainly the effects on blood pressure and unknown risks to cardiovascular health—must be carefully considered.

Notably, the FDA has posed numerous post-marketing inquiries into Contrave\textsuperscript{®}. These post-marketing requirements include additional studies evaluating cardiovascular outcomes, toxicity, potential drug interactions, and use in special populations (pediatric patients, and adult patients with hepatic and/or renal impairment).\textsuperscript{2}
It remains to be seen if Contrave® will become a viable option for weight management in the average overweight or obese patient. The results of Contrave® post-marketing studies will be essential in evaluating the safety of this agent and its place in therapy.

References


Zolpidem Tartrate: Driving Impairment and FDA-Recommended Dosing Changes for Women

Kimberly Mulcahy, PharmD

The Institute of Medicine reports sleep deprivation and sleep disorders are unaddressed public health problems resulting in healthcare consequences and increased healthcare costs.1,2 Patients suffering from sleep disturbances are often prescribed non-benzodiazepine hypnotics, such as zolpidem (Ambien®, Ambien CR®, Edluar®, Zolpimist®, Intermezzo®), eszopiclone (Lunesta®), zaleplon (Sonata®), and zopiclone (Imovane®, not currently available in the United States [US]), commonly referred to as Z-drugs.3 Since its approval in 1992, zolpidem remains the most frequently prescribed sleep aid.1,4

The first dosage form introduced for the treatment of insomnia was Ambien® (zolpidem tartrate). Soon after, additional formulations were created to treat other sleep disturbances: Ambien CR® for difficulty staying asleep and Intermezzo® for middle of the night awakenings.1 New delivery systems Edluar® sublingual tablet and
Zolpimist® oral spray were also created to treat patients who had difficulty falling asleep and were unable to swallow tablets.\(^3\)

Despite the alleviation of sleep disturbances, benzodiazepine receptor agonists including the Z-drugs have an array of side effects pertaining to cognitive impairment, such as next-morning driving impairment, anterograde amnesia, behavioral and cognition changes, reduced decision-making capacity, impaired word call and recognition, and increased risk of falls.\(^1,3,4\) Furthermore, falls among elderly patients are associated with high morbidity including fractures and head injuries and may also be fatal.\(^4\)

In 2013, the Food and Drug Administration (FDA) issued changes in the prescribing information for selected zolpidem-containing products, based on the risk for next-morning impairment.\(^5\) These changes included reduced doses of zolpidem-containing products, with the exception of Intermezzo®, for female patients, as well as updated warnings for next-morning impairment.

Prior to the FDA’s decision to alter the prescribing information for zolpidem-containing products, in early 2007, the FDA had requested stronger labeling for the Z-drugs, including warnings about the risk of complex sleep-related behaviors.\(^2,3,6\) These parasomnias included sleep eating, sleep driving, and cognition and next-day performance impairment.\(^6\) As the newer formulation Intermezzo® was approved in 2011, investigators conducted studies to identify the severity of next-day impairment from zolpidem and the potential relationship between serum concentration of zolpidem and driving impairment.\(^1,6\) Driving has been frequently used as a performance indicator for psychomotor impairment due to the complexity of the task, requiring alertness, reaction times, and spatial awareness, representing overall psychomotor capability.\(^6\) A driving simulation was submitted to the FDA which determined that a serum concentration of zolpidem >50 ng/mL impaired driving ability to a degree that increases the risk of motor vehicle accidents.\(^1,3,6\)

After determining the threshold dose for driving impairment, further pharmacokinetic trials were conducted to determine which doses had the greatest risk for eliciting morning driving impairment.\(^1,5,6\) A total of 250 men and 250 women were given 10 mg of immediate release zolpidem tartrate and blood levels were drawn 8 hours later. Of note, as stated by the manufacturers, zolpidem products should only be used when a patient has 8 hours to devote to sleep.\(^5\) Among the patients, 15% of women and 3% of men had serum concentrations ≥50 ng/mL.\(^3-5\) Adults aged 55-65 years exhibited impairment lasting 10 hours after a 10 mg dose.\(^5\) When the subjects were given 12.5 mg of controlled-release zolpidem, 33% of women and 25% of men had elevated serum concentrations 8 hours post-administration.\(^3-5\) Subjects were also analyzed after taking 6.25 mg of controlled-release zolpidem; 15% of women, 5% of men, and 10% of elderly men and women had serum levels ≥50 ng/mL.\(^1,3,5\)

Driving under the influence of drugs (DUID) has been on the rise since the 1990s and can be explained by the increasing use of prescription medication.\(^1,2,6\) Although driving under the influence of alcohol can be determined by a Breathalyzer and field sobriety tests, it is not as simple to issue a roadside drug test; also, notably, metabolites may remain in the bloodstream long after effects of the medication have worn off. Long-acting benzodiazepines, such as diazepam and clonazepam, are more likely to result in a motor vehicle accidents than short-acting medications.\(^3,7\)

Despite legal limits on blood alcohol concentration (BAC), there are no US traffic laws dictating limits on concentrations of central nervous system (CNS) depressants or psychoactive medications. In Norway, serum concentrations of zolpidem and zopiclone were collected between 2001 and 2010 from peripheral blood samples of impaired drivers and forensic autopsies with cause of death classified as intoxication.\(^8\) There were...
357 deaths attributed to drug intoxication; the median concentration of zolpidem was 300 ng/mL. Among the samples from 837 impaired drivers, the median concentration was 190 ng/mL. Legislation against DUID has since been passed in Norway establishing a limit on zolpidem serum concentration of 31 ng/mL. Notably, the International Council on Alcohol, Drugs and Traffic Safety consider 77 ng/mL and 184 ng/mL to be equivalent to a BAC of 0.05% and 0.12%, respectively.

Currently, zolpidem-containing products and the other non-benzodiazepine hypnotics are only indicated for short-term use. It is unknown if long-term use of the medication results in tolerance to the performance-impairing effects. Patients with long-term use of benzodiazepines develop tolerance to psychomotor impairment; however, results from recent studies suggest that this effect may not be observed with non-benzodiazepine hypnotics.

Due to the slower metabolism of zolpidem by women, the FDA mandated changes in dosing recommendations of zolpidem-containing products for female patients. The recommended dose of immediate-release zolpidem tartrate has been reduced from 10 mg to 5 mg at bedtime, and the recommended dose of controlled-release products has been reduced from 12.5 mg to 6.25 mg at bedtime. No changes were recommended for Intermezzo®. Intermezzo® is supplied as 1.75 mg or 3.5 mg sublingual tablets, and the FDA-approved doses for women and men are 1.75 mg and 3.5 mg, respectively.

Although the dose recommendation change was mandatory for women, there was no required dose change for men, despite both genders maintaining a substantial serum level of zolpidem 8 hours post-dose. Though not required, the FDA advised consideration for usage of lower doses in men: 5 mg of immediate-release and 6.25 mg of controlled-release zolpidem.

Overall, the FDA recommends that all patients receiving zolpidem-containing drugs be maintained at the lowest effective dose and to consider lowering doses for all patients.

References

5. Food and Drug Administration (FDA). FDA drug safety communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR. Available at: [http://www.fda.gov/drugs/drugsafety/ucm352085.htm](http://www.fda.gov/drugs/drugsafety/ucm352085.htm). Accessed February 10, 2015.
6. Kuehn BM. FDA warning: driving may be impaired the morning following sleeping pill use. *JAMA.* 2013;309(7):645-646.
Breaking Down the Updated ACIP Recommendations for Pneumococcal Vaccination in Adults Aged ≥65 Years

Lisa Garza, PharmD

Overview

On August 13, 2014, the Centers for Disease Control and Prevention (CDC)-Advisory Committee on Immunization Practices (ACIP) updated the recommendations for 13-valent pneumococcal conjugate vaccine (PCV13 or Prevnar 13®).1 Previously, PCV13 use had been limited to the pediatric population or immunocompromised adults. The new recommendations from ACIP expand the use of PCV13 to include routine administration in series with the 23-valent pneumococcal polysaccharide vaccine (PPSV23 or Pneumovax® 23) for adults aged ≥65 years.

Background

What are the differences between PCV13 and PPSV23?

PCV13 is a conjugated vaccine that contains 13 Streptococcus pneumoniae serotypes; PPSV23 is a polysaccharide vaccine that contains 23 S. pneumoniae serotypes.2,3 The serotypes included in PCV13 are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.2 PCV13 and PPSV23 have 12 serotypes in common; 6A is the additional serotype in PCV13 not included in PPSV23. Serotype 6A accounted for 9.5% of invasive pneumococcal disease (IPD) cases in adults aged ≥65 years from 2006-2007.2,4

What were the previous recommendations for using PCV13 in older adults?

PCV13 was approved by the Food and Drug Administration (FDA) in 2011 for prevention of pneumonia and invasive disease caused by the included S. pneumoniae serotypes in adults aged ≥50 years.5 However, until this year, ACIP had only recommended PCV13 use in adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid (CSF) leaks, or cochlear implants.1,6

For more information on the FDA approval history and CDC-ACIP recommendation history of PCV13, see Figure 1.

New ACIP Recommendations

What are the latest recommendations?

The ACIP recommends routine use of PCV13 in series with PPSV23 in adults aged ≥65 years.1 PCV13 and PPSV23 should be given at least 8 weeks apart, ideally 6-12 months apart. PCV13 should be given first; studies evaluating subjects receiving the vaccines in series have demonstrated higher antibody responses in subjects receiving PCV13 followed by PPSV23 1 year later compared to those receiving PPSV23 followed by PCV13. Patients aged ≥65 years are eligible for PCV13 vaccination whether they are vaccine-naïve or have already received PPSV23. Patients with an unknown vaccination history should be considered vaccine-naïve. Figure 2 outlines these recommendations.
Figure 1. Timeline of FDA indication approvals and CDC-ACIP recommendations for PCV13.\textsuperscript{1,5-7}

*Underlying medical conditions that increase the risk for pneumococcal disease include 1) immunocompetent children with chronic heart disease, chronic lung disease, diabetes mellitus, cerebrospinal fluid leaks and cochlear implants, 2) children with functional or anatomic asplenia and 3) children with immunocompromising conditions.

**Approved disease states noted are only those caused by the 13 \textit{Streptococcus pneumoniae} serotypes included in the vaccine.

Figure 2. Sequential administration and recommended intervals for PCV13 and PPSV23 for adults aged ≥65 years.\textsuperscript{1}
Why are the recommendations coming out now?

PCV13 use in adults aged ≥50 years was instituted in 2011 through the FDA accelerated approval pathway. The ACIP deferred establishment of recommendations for use of PCV13 in adults aged ≥65 years pending the availability of clinical data in this population.

What data are available to support the new recommendations?

Previous data in children demonstrated conjugate vaccines to be effective against IPD, community-acquired pneumonia (CAP), and otitis media. More recently, studies have been conducted evaluating the efficacy of these vaccines in adults. Notably, the ACIP recommendation regarding the use of PCV13 in adults aged ≥65 years was based on findings from the CAP immunization trial in adults (CAPiTA).

CAPiTA was a randomized, placebo-controlled trial conducted in the Netherlands between 2008 and 2013. The primary objective of the study was to demonstrate efficacy of PCV13 in the prevention of a first episode of vaccine-type pneumococcal CAP. The secondary objectives were to demonstrate efficacy in prevention of a first episode of nonbacteremic/noninvasive vaccine-type pneumococcal CAP and of vaccine-type IPD.

This study included approximately 85,000 adults aged ≥65 years. The trial demonstrated that PCV13 was 45.6% (95% confidence interval [CI]: 21.8-62.5) effective against vaccine-type pneumococcal pneumonia, 45.0% (95% CI: 14.2-65.3) effective against vaccine-type nonbacteremic pneumococcal pneumonia, and 75.0% (95% CI: 41.4-90.8) effective against vaccine-type IPD among adults aged ≥65 years. These differences were determined to be clinically significant.

What is the benefit of the new recommendations to patients?

*Streptococcus pneumoniae* remains a leading cause of serious illness and is of global concern. In the United States, the number of deaths due to pneumococcal disease exceeds that of all other vaccine-preventable illnesses combined. According to the CDC, in 2013, an estimated 13,500 cases of IPD occurred among adults aged ≥65 years. Approximately 20-25% of IPD cases and 10% of CAP cases in adults aged ≥65 years are caused by serotypes contained in PCV13; these cases may be prevented with the use of PCV13 in this population.

Although PCV13 and PPSV23 have 12 S. pneumonia serotypes in common, studies comparing PCV13 to PPSV23 have shown similar immunogenic responses for 2 serotypes and higher responses for 10 serotypes in adults aged ≥70 years receiving PCV13.

**Practical Points**

How is PCV13 administered in adults?

PCV13 should be administered intramuscularly, as a single dose of 0.5 mL with a ½ to 1½ inch-length needle. The vaccine is supplied in prefilled syringes and contains no thimerosal preservative.

What are common side effects of the vaccine?

Common adverse events with PCV13 include the following:

- Pain, redness, and swelling at the injection site
- Limitation of movement of the arm in which the injection was given
- Fatigue
- Headache
- Chills
- Decreased appetite
- Generalized muscle pain
- Joint pain

Similar adverse reactions have been reported among adults receiving PCV13 and PPSV23.¹

**Which patients aged ≥65 years should NOT be given PCV13?**

PCV13 is contraindicated in patients with a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or any diphtheria toxoid-containing vaccine.² Based on the updated recommendations, PCV13 should not be given to patients who have received PPSV23 within 1 year.¹

**Can PCV13 be given with other vaccines?**

Concomitant administration of PCV13 with other vaccines has only been studied with the trivalent inactivated influenza vaccine (TIV).¹ According to the CDC, concomitant administration of PCV13 with TIV was demonstrated to be safe and immunogenic. However, immunogenic markers for both vaccines were reduced with PCV13 plus TIV versus PCV13 or TIV alone.

Concomitant administration of vaccines may be associated with an increased risk of local reactions (e.g., mild redness) and systemic reaction (e.g., headache, chills, decreased appetite and joint pain).²

**What is the cost of PCV13? Is it covered by Medicare?**

Despite the recommendations, vaccine uptake may be limited due to cost. The manufacturer-reported cost is approximately $152 per dose.¹⁰ The Pfizer Pathways Patient Assistance Program offers PCV13 at no cost to individuals aged >19 years who are uninsured or lack coverage for Prevnar 13®, and meet income criteria. However, the program requires administration of the vaccine in a clinic.

Medicare coverage has been recently updated; the program will cover the cost of 2 pneumonia vaccines, effective on or after September 19, 2014.¹¹ The second vaccine will be covered, provided at least 11 full months has elapsed since administration of the first vaccine. This modification was to be implemented February 2, 2015.

**Take Away Messages**

- In 2014, the ACIP updated its recommendations for pneumococcal vaccination to include routine use of PCV13 in series with PPSV23 in adults aged ≥65 years.
- The recommendations are supported by data from a large-scale clinical trial demonstrating reduced incidence of IPD and CAP with administration of PCV13 in patients aged ≥65 years.
- Medicare Part B will cover 2 doses of pneumococcal vaccination given 12 months apart, effective September 19, 2014.
Pharmacists and providers should work together to raise awareness that patients may need PCV13 for additional pneumococcal coverage and to find ways to reduce the cost burden of this vaccine to patients.

References


Recommendations from the Sexually Transmitted Infection 2014 Draft-Guidelines

Holly Hamilton, PharmD

Physicians and other healthcare providers, including pharmacists, play a critical role in preventing and treating sexually transmitted infections (STIs). The Centers for Disease Control and Prevention (CDC) have worked with healthcare providers to create comprehensive guidelines on the treatment of STIs in the United States (US). The CDC published treatment guidelines in 2010 and issued an updated draft in 2014; the draft is currently under peer-review. Changes proposed in the new guidelines include:

- Updated alternative treatment regimens for Neisseria gonorrhoeae and genital warts
- Updated trichomoniasis and urethritis diagnostics
- Discussion of the role of *Mycoplasma genitalium* in urethritis/cervicitis and treatment-related implications
- Updated counseling points on human papillomavirus (HPV)
- A new section on the management of transgender individuals
- Recommendations for annual testing for hepatitis C in persons with human immunodeficiency virus (HIV) infection, and
- Recommendations on retesting after treatment to detect repeat infection.

In this review, some of the most commonly diagnosed STIs and the recommendations on their treatment will be presented. The complete draft-guidelines may be accessed at [http://www.cdc.gov/std/treatment/update.htm](http://www.cdc.gov/std/treatment/update.htm).

**Syphilis**

Syphilis is a systemic disease caused by *Treponema pallidum*. Syphilis is divided into stages to guide treatment and follow-up. Signs and symptoms of primary, secondary, and tertiary syphilis are outlined in Table 1. Latent syphilis is characterized by absence of symptoms and may be detected by serology early on or as late as 10 to 30 years after the initial infection.

**Diagnosis:** There are 2 types of serologic tests for syphilis: non-treponemal (e.g., rapid plasma reagin) and treponemal (e.g., fluorescent treponemal antibody absorbed). Most patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity. False-positive non-treponemal results can be associated with various medical conditions unrelated to syphilis, including infectious diseases such as HIV, autoimmune conditions, immunizations, pregnancy, and old age. The CDC advises use of both non-treponemal and treponemal testing in the diagnosis of syphilis due to the risks for false-negative and false-positive results. If a patient has a negative result with a non-treponemal test, use of a treponemal test as a repeat is recommended. Even if serologic tests are negative, if clinical findings are suggestive of syphilis, presumptive treatment and alternative testing are recommended.

**Follow-up:** Patients should return for follow-up serologic non-treponemal testing at 6 and 12 months after treatment. Patients with neurosyphilis should return for additional follow-up at 24 months. There is limited information regarding the follow-up required for individuals with tertiary syphilis. Professional judgment is advised with these patients. Individuals who have signs or symptoms that persist or recur, or who have a sustained 4-fold increase in non-treponemal test titer may have failed treatment or developed re-infection.
Table 1. Overview of syphilis presentation and treatment in selected populations.1

<table>
<thead>
<tr>
<th>Signs/symptoms</th>
<th>Primary</th>
<th>Secondary</th>
<th>Tertiary</th>
<th>Latent</th>
<th>Neuro</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ulcers or chancres at infection site</td>
<td>Skin rash, lymphadenopathy, mucocutaneous lesions</td>
<td>Cardiac lesions</td>
<td>Only detectable via laboratory testing</td>
<td>Cranial nerve dysfunction, meningitis, stroke, AMS</td>
</tr>
<tr>
<td>Adult treatment</td>
<td>Benzathine penicillin G 2.4 million units IM x 1 dose</td>
<td>Benzathine penicillin G 2.4 million units IM x 1 dose</td>
<td>Benzathine penicillin G 2.4 million units IM weekly x 3 doses</td>
<td>Early - Benzathine penicillin G 2.4 million units IM x 1 dose</td>
<td>Late - Benzathine penicillin G 2.4 million units IM weekly x 3 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aqueous crystalline penicillin G 3–4 million units IV every 4 hours or 18-24 million units per day by continuous infusion x 10–14 days</td>
</tr>
<tr>
<td>Alternative treatment options*</td>
<td>Doxycycline 100mg PO BID x 14 days</td>
<td>Doxycycline 100mg PO BID x 14 days</td>
<td>Consult an ID specialist</td>
<td>Doxycycline 100mg PO BID x 28 days</td>
<td>Ceftriaxone 2g IM or IV daily x 10-14 days</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone 1-2g IM or IV daily</td>
<td>Ceftriaxone 1-2g IM or IV daily</td>
<td></td>
<td>Tetracycline 500mg PO QID x 28 days</td>
<td>(limited data available)</td>
</tr>
<tr>
<td>Treatment in pregnancy</td>
<td>Patients with syphilis who are pregnant should be desensitized to penicillin and treated with penicillin. Desensitization protocols are available in the guidelines at the link listed in the beginning of this review.</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

AMS=altered mental status; IM=intramuscular; IV=intravenous; PO=by mouth; BID=twice daily; ID=infectious diseases; QID=4 times daily
*May be considered in patients with penicillin allergy. Rule out pregnancy for doxycycline and tetracycline.

Clinical Pearls:
- Penicillin G should be used in all cases of syphilis in pregnancy. If a pregnant patient is penicillin-allergic, desensitization should be performed. Desensitization instructions are available in the full draft-guidelines.1,3
- The Jarisch-Herxheimer reaction is a reaction that occurs within 24 hours after the initiation of syphilis therapy.1 Symptoms of this reaction include headache, myalgia, fever, and other nonspecific findings. This reaction occurs most frequently among persons who have early syphilis. Antipyretics can be used to manage symptoms.
- Selection of the appropriate penicillin preparation is important, due to differences among the medications in distribution and extent of penetration into the infection site.1
- Combination therapy is not recommended. Practitioners have inadvertently prescribed combination benzathine-procaine penicillin (Bicillin C-R) instead of benzathine penicillin (Bicillin L-A).1 Pharmacists should be aware of the similarity in names and recognize benzathine as the appropriate agent.6

Chlamydia

Chlamydia is the most commonly reported STI in the US with the highest prevalence in patients aged ≤24 years.1 The disease is caused by Chlamydia trachomatis. Patients with chlamydia may present without symptoms, regardless of gender. However, if untreated, sequelae such as pelvic inflammatory disease (PID) and infertility may develop.7
Diagnosis: Chlamydia can be diagnosed by testing first-catch urine or by collecting swab specimens from either the endocervix or vagina in women, or the urethra in men.\(^1\)

**Table 2. Overview of chlamydia treatment.\(^1\)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Azithromycin 1g PO x 1 dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doxycycline 100mg PO BID x 7 days</td>
</tr>
<tr>
<td>Alternative treatment options</td>
<td>Erythromycin base 500mg PO QID x 7 days</td>
</tr>
<tr>
<td></td>
<td>Erythromycin ethylsuccinate 800mg PO QID x 7 days</td>
</tr>
<tr>
<td></td>
<td>Levofoxacin 500mg PO daily x 7 days</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Ofloxacin 300mg PO BID x 7 days</td>
</tr>
</tbody>
</table>

**Treatment in pregnancy**

Azithromycin 1g PO x 1 dose

PO=by mouth; BID=twice daily; QID=4 times daily

Follow-up: Repeat testing is not recommended unless patient adherence to treatment is questionable, the patient continues to have symptoms, and/or re-infection is suspected.\(^1\)

Clinical Pearls:

- Azithromycin may be cost-effective in treating chlamydia because only 1 dose is required; this may be optimal for patients with barriers to adherence.\(^8\)
- Individuals should be instructed to abstain from sexual intercourse for 7 days after single-dose therapy or completion of a 7-day regimen, and until all of their sex partners are treated.\(^1\)

Gonorrhea

Gonorrhea is the second most commonly reported STI in the US with an incidence of 82,000 cases per year.\(^1,7\) This infection is caused by *Neisseria gonorrhoeae*. Symptoms are generally absent in women; however, in men, symptoms such as unusual discharge and pain have been reported. Due to the asymptomatic nature of this infection in women, it is generally not diagnosed until patients develop complications such as PID or tubal scarring. Patients at high risk for gonorrhea infection include women aged <25 years of age, with new or multiple sex partners, previous gonorrhea infection, or other STIs. Additional high risk groups include those who engage in commercial sex work and illicit drug use, women of certain demographic backgrounds, those living in communities with a high prevalence of disease, and subgroups of men who have sex with men (MSM) population. Routine screening is not recommended in patient populations that are not considered high risk.\(^9\)

Diagnosis: Diagnosis should be performed by culture of female endocervical or male urethral swab specimens.\(^1\) Nucleic acid amplification tests (NAAT) are also available for detection of *N. gonorrhoeae*; collection methods and types of specimen for each NAAT may vary, as well as the level of sensitivity.

Changes in Treatment: Over the last decade, there has been increasing concern regarding *N. gonorrhoeae* resistance in the US and other countries throughout the world.\(^10\) In 2007, the CDC no longer recommended fluoroquinolones for treatment of gonorrhea due to increasing resistance in this drug class.\(^11\) With the same resistance concerns in the cephalosporin drug class, the 2010 STI treatment guidelines recommended dual therapy for gonorrhea infections.\(^12\) The preferred first-line regimen included a cephalosporin plus either azithromycin or doxycycline. From 2006 to 2011, the minimum inhibitory concentrations (MICs) of in vitro *N. gonorrhoeae* increased, thus forcing the CDC to question the efficacy of cefixime, the standard cephalosporin
used to treat gonorrhea in many institutions.\textsuperscript{7,13} Because of the change in MICs, the CDC no longer recommends the use of cefixime as a first-line agent. In addition to resistance to fluoroquinolones and cefixime, tetracycline resistance is also being noted in many countries as well.

Currently, the only first-line, dual regimen that is recommended for treatment of gonorrhea in the US is ceftriaxone and azithromycin.\textsuperscript{1}

It is important to note that gonorrhea infection can occur in and is classified by various parts of the body; however, treatment for this infection does not change based on its location.\textsuperscript{1}

Table 3. Overview of gonorrhea treatment.\textsuperscript{1}

<table>
<thead>
<tr>
<th>Treatment for uncomplicated infection</th>
<th>Ceftriaxone 250mg IM x 1 dose PLUS Azithromycin 1g PO x 1 dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative treatment options</td>
<td>Cefixime 400mg PO x 1 dose PLUS Azithromycin 1g PO x 1 dose</td>
</tr>
<tr>
<td>Treatment in pregnancy</td>
<td>Azithromycin 1g PO x 1 dose</td>
</tr>
</tbody>
</table>

IM=intramuscular; PO=by mouth

Follow-up: Repeat testing is generally not recommended unless the patient has a suspected treatment failure.\textsuperscript{1}

If the patient has been treated with an alternative regimen for pharyngeal gonorrhea, they should return for repeat testing 14 days after treatment.

Clinical Pearls:

- All individuals being tested or treated for gonorrhea should be tested for other STIs, including chlamydia and syphilis.\textsuperscript{1}
- Ceftriaxone and azithromycin should be administered on the same day, preferably at the same time.\textsuperscript{1}

Bacterial Vaginosis (BV)

BV is a syndrome resulting from replacement of Lactobacillus in the vagina with high concentrations of anaerobic bacteria (e.g., Prevotella sp. and Mobiluncus sp.), G. vaginalis, Ureaplasma, Mycoplasma, and many others.\textsuperscript{1} Most women who experience BV are asymptomatic; however, BV is a common cause of unusual vaginal discharge and malodor.\textsuperscript{14} Risk factors for BV include multiple male or female partners, a new sex partner, douching, lack of condom use, and lack of vaginal Lactobacilli. Women who have never been sexually active are rarely affected.\textsuperscript{15}

Diagnosis: BV can be diagnosed by clinical criteria or Gram stain.\textsuperscript{16} A clinical diagnosis requires 3 of the following symptoms or signs:

- Homogeneous, thin, white discharge that smoothly coats the vaginal walls
- Presence of clue cells on microscopic examination
- Vaginal fluid pH >4.5, or
- A fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test).
Table 4. Overview of BV treatment.1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole 500mg PO BID x 7 days</td>
<td>Metronidazole 0.75% gel, 1 full applicator intravaginally daily x 5 days</td>
</tr>
<tr>
<td>Metronidazole 0.75% gel, 1 full applicator intravaginally daily x 5 days</td>
<td>Clindamycin 2% cream, 1 full applicator intravaginally at bedtime x 7 days</td>
</tr>
<tr>
<td>Alternative treatment options</td>
<td>Alternative treatment options</td>
</tr>
<tr>
<td>Tinidazole 2g PO daily x 2 days</td>
<td>Tinidazole 1g PO daily x 5 days</td>
</tr>
<tr>
<td>Tinidazole 1g PO daily x 5 days</td>
<td>Clindamycin 300mg orally twice daily for 7 days</td>
</tr>
<tr>
<td>Clindamycin 300mg orally twice daily for 7 days</td>
<td>OR</td>
</tr>
<tr>
<td>OR</td>
<td>Clindamycin ovules 100mg intravaginally at bedtime for 3 days</td>
</tr>
<tr>
<td>Treatment in pregnancy</td>
<td>Treatment in pregnancy</td>
</tr>
<tr>
<td>Because oral therapy has not been shown to be superior to topical therapy for treating symptomatic BV, symptomatic pregnant women can be treated with either of the oral or vaginal regimens recommended for non-pregnant women.</td>
<td>PO=by mouth; BID=twice daily</td>
</tr>
</tbody>
</table>

Follow-up: Follow-up is not necessary if symptoms resolve.1

Clinical Pearls:
- Alcohol consumption should be avoided during treatment with metronidazole and for 24 hours thereafter to reduce the risk of a disulfiram-like reaction.1 Alcohol consumption should also be avoided during treatment with tinidazole and for 72 hours thereafter.
- Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for 5 days after use.1
- Women should be advised to refrain from sexual activity or use condoms during treatment.1
- Douching may increase the risk for relapse.1

Trichomoniasis

Trichomoniasis is caused by *Trichomonas vaginalis*. Trichomoniasis is one of the most prevalent STIs, affecting an estimated 3.7 million people in the US.17 Symptoms are gender-specific and include urethritis, epididymitis, or prostatitis in males, and vaginal discharge that may be diffuse, malodorous, or yellow-green with or without vulvar irritation in females. However, the majority of infected individuals report minimal or no symptoms.

Diagnosis: The most common diagnostic test used is a wet mount preparation from vaginal secretions.1 The use of highly sensitive and specific tests, such as NAATs and other ribonucleic acid and deoxyribonucleic acid assays, are encouraged due to the poor sensitivity and specificity of the wet mount preparations. However, these highly sensitive and specific tests are more costly and may be less readily available than the materials used for wet mount preparations.

Changes in Diagnostics: The updated recommendations prefer NAATs over microscopy due to increased sensitivity and specificity.1 NAATs will likely be more widely used after the release of the upcoming recommendations.
Table 5. Overview of trichomoniasis treatment.\(^1\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Metronidazole 2g PO x 1 dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative treatment option</td>
<td>Tinidazole 2g PO x 1 dose</td>
</tr>
<tr>
<td>Treatment in pregnancy</td>
<td>Metronidazole 500mg PO BID x 7 days</td>
</tr>
<tr>
<td></td>
<td>Metronidazole 2g PO x 1 dose</td>
</tr>
</tbody>
</table>

PO=by mouth; BID=twice daily

Follow-up: Repeat testing is recommended every 3 months after treatment.\(^1\)

Clinical Pearls:
- Alcohol consumption should be avoided during treatment with metronidazole or tinidazole and for 24 hours or 72 hours post-treatment, respectively, to reduce the risk of a disulfiram-like reaction.\(^1\)
- Metronidazole gel is not recommended because it is less efficacious than oral metronidazole. The gel does not achieve therapeutic levels in the urethra and perivaginal glands.\(^1\)

Summary

In this review, some of the most commonly diagnosed STIs and the updated recommendations on their treatment have been presented. The proposed changes for most of the disease states discussed pertain to diagnostics and alternative treatment options; additional changes have been proposed for other STIs. Changes in these recommendations are important for pharmacists because they have a direct impact on the way that patients are managed. Pharmacists can expect to see changes with treatment regimens and should include proper counseling points when conversing with the patient.

Importantly, the draft-guidelines is currently under peer review, and these recommendations may be subject to further change. Release of the finalized guidelines is expected sometime this year.

References


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Dr. Lindenau completed his undergraduate bachelor’s degree in Biological Sciences at the University at Buffalo and received his Doctor of Pharmacy degree from D’Youville College School of Pharmacy. He is currently a PGY-1 community pharmacy practice resident at the UB/Middleport Family Health Center. Dr. Lindenau has several years of experience in both hospital and community pharmacy. He has plans to practice in the ambulatory care or independent pharmacy setting upon completion of his residency program.

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