Adult Immunizations for Immunocompromised Patients in the Primary Care Setting

Wendy Lantaff, PharmD

The Advisory Committee on Immunization Practices (ACIP) Recommended Adult Immunization Schedule1 for the United States can be generally summarized in a table by recommended vaccine and indicated age group. However, several vaccines have additional, non-age-based indications due to patient-specific risk factors. Furthermore, recent updates have been made to the recommendation schedule to provide further protection for specific patient populations. One population with different immunization needs are the immunosuppressed. Patients with immunosuppressive disorders or those on immunosuppressive medication regimens have more complex immunization needs than patients who are considered immunocompetent. Subsequently, these patients require additional vaccinations to protect themselves from preventable illnesses. While vaccination rates have improved overall in recent years, they still remain low in these patients.

A number of conditions encountered in the primary care setting are considered immunosuppressive: post-transplant patients, those with HIV and patients with immune-mediated diseases are just a few of the conditions that can increase the risk of infection.2-4 While the immunization needs of pre-transplant patients and those with active cancer are important, they are not commonly managed in the primary care setting and therefore are not discussed further in this review. Patients who are post-kidney, post-liver and post-heart transplant are referred to as solid organ transplant recipients, whereas patients who have received a blood- or marrow-derived hematopoietic stem cell transplant are referred to as a hematopoietic cell transplant (HCT) recipients. Diseases that are considered immune-mediated include rheumatoid arthritis (RA), irritable bowel disease (IBD), plaque psoriasis, and psoriatic arthritis. The Box lists commonly prescribed immunosuppressing medications. The purpose of this review is to describe the immunocompromised states for which patients would benefit from an enhanced or alternate immunization schedule.

**INACTIVE VACCINES**

Inactive vaccines are considered safe for immunocompromised patients. However, because immunocompromised patients are at an increased risk of developing an infection or decreased humoral response to vaccination, an enhanced immunization schedule is recommended for these patients. Table 1 summarizes

**Box | Immunosuppressant medication regimens.**

- Azathioprine
- Cyclosporine
- Glucocorticoids (≥20 mg/day prednisone equivalent)
- Hydroxychloroquine sulfate
- Leflunomide
- Methotrexate >4 mg/kg/week
- Mycophenolate mofetil
- Sulfasalazine
- Tacrolimus
- Tumor necrosis factor (TNF) inhibitors (e.g., etanercept, infliximab, adalimumab, certolizumab pegol, golimumab)
- Other biologics (e.g., anakinra, canakinumab, tocilizumab, abatacept, rituximab)
the 2013 ACIP recommendations for inactive vaccinations. Unfortunately, current data suggest that some immunocompromised patients are undervaccinated. One study revealed that 86% of patients with IBD report using immunosuppressive medications; however, of these immunocompromised patients, less than 10% had received the 23-valent pneumococcal polysaccharide (PPSV23) vaccine. The 13-valent pneumococcal conjugate (PCV13) was not evaluated, as it was not recommended by the ACIP at the time the study was published. Considering most IBD patients will eventually be on immunosuppressive agents, the PCV13 vaccine and the PPSV23 vaccine could be considered appropriate for all patients with a diagnosis of IBD. Similarly, the American College of Rheumatology (ACR) recommends that RA patients on a disease modifying anti-rheumatic drug (DMARD) (hydroxychloroquine, leflunomide, methotrexate, minocycline, or sulfasalazine) should be given the PPSV23 vaccine, regardless of their current state of immunosuppression. However, the PCV13 should only be given to RA patients who are on an immunosuppressive medication regimen.

Although the high-dose inactivated influenza vaccine (60 mcg of antigen per strain) is currently only approved for persons ≥65 years, the increased antigen concentration may be beneficial for certain immunocompromised patients because the higher concentrations result in an increased immune response, thereby providing additional protection from influenza. The safety and immune response of the high-dose inactive influenza immunization was evaluated in immunosuppressed HIV positive patients. Participants of this study received either the standard-dose (15 mcg of antigen per strain) or high-dose influenza vaccine. Both groups reported similar mild adverse events, while the rate of antibody titers was greater in the high-dose group. Although further research is needed before a universal recommendation can be made, using the high-dose influenza vaccine in HIV patients and some other immunocompromised patients under 65 years may provide additional protection.

In contrast to most other cohorts, persons who are post-solid organ transplant should wait 3 to 6 months post-transplant, or once the patient has reached their maintenance dose of their immunosuppressive medications before inactive vaccinations are administered. Although the antibody response in post-solid organ transplant patients varies after the administration of the inactivated influenza vaccine, it has demonstrated consistent and sufficient protection against influenza for the duration of the year, thus, a second vaccine administered during the same season is not needed for the solid organ transplant population.

Similar to post-solid organ transplant patients, post-HCT patients should wait 6 months before most inactive vaccinations are administered. Although the level of immunosuppression at <6 months post-HCT is too great for the patient to mount an adequate immune response, vaccination may be performed during an influenza outbreak, because some protection may be conveyed. HCT patients should receive a booster dose of the influenza vaccine if the first dose was received within 6 months post-transplant.

If an immunocompromised patient had an interrupted or incomplete inactive vaccine series, the current recommendation is to complete only the incomplete portion of the series without any additional booster vaccinations, or repetition of past doses. However, for post-transplant patients, booster vaccination may be warranted based on titers. If checking titers after vaccination, a minimum of 4 weeks should have elapsed between the vaccination and the titer. Further, regardless of titers, post-HCT patients should also receive the entire tetanus, diphtheria and pertussis series post-transplant.

### Live Vaccines

In contrast, live vaccinations are contraindicated in immunocompromised patients. This contraindication is because immunocompromised individuals are at increased risk of infection due to their inability to mount an adequate immune response against the live vaccine. However, due to the increased risk of these patients developing a vaccine preventable infection, care must be taken when evaluating a patient’s immunosuppressive status. The degree of immunosuppression resulting from immunosuppressive drugs and conditions varies. The 2013 ACIP recommendations are summarized in Table 1.

Patients over the age of 50 years could be candidates for the herpes zoster vaccine, and the administration of this vaccine should be closely evaluated in patients with some degree of immunosuppression, because patients with immune-mediated diseases have an increased incidence of herpes zoster infection. Although many of the immunosuppressive medication regimens are contraindicated for the receipt of live vaccines, the degree of immunosuppression needs to be assessed, because mild immunosuppressants may not preclude herpes zoster vaccination. For example, patients with RA or other immune-mediated diseases taking low-dose methotrexate or glucocorticoid steroids...
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>ACIP General Recommendation</th>
<th>Recommendation for Immunocompromised Patients</th>
<th>Revaccination Indicated for the Immunocompromised</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inactivated vaccines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Influenza</strong></td>
<td>All patients should receive the influenza vaccine annually.</td>
<td>Should only receive inactivated vaccine.</td>
<td>Second dose for HCT recipients who received vaccine &lt;6 months after transplant.</td>
</tr>
<tr>
<td><strong>PPSV23</strong></td>
<td>All adults ≥ 65 years should be vaccinated. Adults 19-64 years with immunocompromising conditions, including immunosuppressive medications or: chronic heart disease, chronic lung disease, diabetes mellitus, cerebrospinal fluid leak, cochlear implant, alcoholism, chronic liver disease or cirrhosis, cigarette smoking, or functional or anatomic asplenia.</td>
<td>Should receive the PPSV23 vaccine and the PCV13 vaccine. For patients who have not received any pneumococcal vaccine, PCV13 should be administered first, followed by the PPSV23 28 weeks later. If the patient has previously been vaccinated with PPSV23, they should receive a dose of PCV13 ≥1 year later.</td>
<td>One-time revaccination with PPSV23 5 years after first dose, regardless of age, then again at age ≥65 years if ≥5 years since previous PPSV23.</td>
</tr>
<tr>
<td><strong>PCV13</strong></td>
<td>Adults ≥ 19 years with immunocompromising conditions, including those on immunosuppressive medications, functional or anatomic asplenia, cerebrospinal fluid leaks or cochlear implants.</td>
<td></td>
<td>Revaccination is not recommended at this time.</td>
</tr>
<tr>
<td><strong>Hepatitis A</strong></td>
<td>Adults who want to be protected and those with risk factors: travelers or workers in at-risk countries, adults adopting a child from a country of high or intermediate prevalence, chronic liver disease, drug abuser, men who have sex with men, food handlers, and laboratory workers who work with the hepatitis virus.</td>
<td>Should receive the hepatitis A vaccine if desired by the patient or if the patient has additional risk factors.</td>
<td>Presence of additional risk factors warrants monitoring titers yearly for solid organ transplant/HCT recipients and revaccination as needed.</td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>Adults wanting protection and those with risk factors: sexually active people not in a long-term, mutually monogamous relationship; men who have sex with men; people with HIV; patients seeking STD evaluation or treatment; injection drug users; renal disease that may progress to dialysis; dialysis; healthcare personnel and public safety workers; inmates in correctional facilities; travelers to countries with an intermediate or high prevalence of hepatitis B, and household contacts and sex partners of HBsAg-positive people.</td>
<td>Should receive the hepatitis B vaccine if desired by the patient or if the patient has additional risk factors.</td>
<td>For solid organ transplant/HCT recipients monitor titers every 12 months and revaccination as needed.</td>
</tr>
<tr>
<td><strong>Td/Tdap</strong></td>
<td>Adults who completed the primary vaccination series should receive a booster vaccination every ten years with Td or one dose of Tdap if they have not previously received it. Pregnant women should be administered Tdap regardless of time since previous vaccination.</td>
<td></td>
<td>HCT patients should repeat the primary series starting 6 – 12 months post-transplant.</td>
</tr>
<tr>
<td><strong>HPV</strong></td>
<td>Previously unvaccinated adult men 19–21 years and women 19–26 years should complete the 3 dose series.</td>
<td>Men ≤26 years should complete the series.</td>
<td>Revaccination not recommended.</td>
</tr>
<tr>
<td><strong>Meningococcal</strong></td>
<td>First-year college students living in residence halls and adult patients with risk factors: microbiologists routinely exposed to isolates of Neisseria meningitides, military recruits and persons who travel to or live in countries where meningococcal disease is prevalent.</td>
<td></td>
<td>Patients with HIV who are candidates for the vaccine should receive two doses.</td>
</tr>
</tbody>
</table>

PPSV23 = 23-valent pneumococcal polysaccharide vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; Td/Tdap = Tetanus, diphtheria, pertussis; HPV = human papillomavirus; MMR = measles, mumps, rubella.
are not considered to be immunosuppressed and should be given the herpes zoster vaccine at ages >50 years old, when the risk of acquiring a herpes zoster infection increases. The ACR also recommends patients be given the herpes zoster vaccine 4 to 6 weeks prior to starting biologic therapy if their age indicates receiving the vaccine. Six percent of the patients received the herpes zoster vaccine during the study. Of the subset of patients taking an immunosuppressive biologic medication regimen, and in whom the vaccine was contraindicated, 63 received the herpes zoster vaccination. To evaluate safety, the study reviewed cases of herpes zoster which occurred within 42 days after the 42-day efficacy window; however, the usual relationship between vaccination and infection was not established. In contrast, no patients who received the herpes zoster vaccine while on a biologic medication regimen developed herpes zoster infection during this time. Further, after the 42-day efficacy window, herpes zoster infection was significantly reduced overall by 39% in patients who received the herpes zoster vaccine while taking biologics, DMARDs and/or glucocorticoid steroids. Although further studies are needed to evaluate the safety and efficacy of the herpes zoster vaccine, in patients with immune-mediated diseases who are taking biologic therapy, the evidence suggests the vaccine is beneficial in these patients. Until more evidence is available, for patients with immune-mediated diseases currently taking biologic medications or immunosuppressive doses of glucocorticoids, a medication break may be considered so the herpes zoster vaccine can be administered. The general recommendation is to wait three months from when the next dose of the biologic medication is scheduled, regardless of the biologic medication, prior to receiving the herpes zoster vaccine. However, if the next dose of the biologic medication is not scheduled until three months from the herpes zoster vaccine, the patient can be safely administered a dose of the herpes zoster vaccine prior to the next dose of the biologic medication. When the herpes zoster vaccine is administered to a patient who has not received their biologic medication, the evidence suggests the vaccine can be safely administered to these patients. Table 1 (cont'd) | 2013 Advisory Committee on immunization practices summary recommendations for inactivate and active vaccines.

<table>
<thead>
<tr>
<th>Vaccine</th>
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<th>Revaccination Indicated for the Immunocompromised</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live vaccines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>Immunocompetent adults without evidence of immunity should receive two doses.</td>
<td>Contraindicated in immunosuppressed patients with the exception of those with HIV and a CD₄⁺ lymphocyte count &gt;200 cells/µL.</td>
<td>Vaccination is contraindicated.</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>Adults ≥60 years (FDA approved for ≥50 years) who are immunocompetent.</td>
<td>Contraindicated in immunosuppressed patients. No recommendation for patients with HIV and a CD₄⁺ lymphocyte count &gt;200 cells/µL.</td>
<td>Vaccination is contraindicated.</td>
</tr>
<tr>
<td>MMR</td>
<td>Adults born after 1957 should receive the series if they have no laboratory evidence of immunity and no contraindication to receiving the vaccine.</td>
<td>Contraindicated in immunosuppressed patients with the exception of those with HIV and a CD₄⁺ lymphocyte count &gt;200 cells/µL.</td>
<td>Vaccination is contraindicated.</td>
</tr>
</tbody>
</table>

PPSV23 = 23-valent pneumococcal polysaccharide vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; Td/Tdap = Tetanus, diphtheria, pertussis; HPV = human papillomavirus; MMR = measles, mumps, rubella.
half-lives of the drug, which would shorten the duration of the medication break in many cases. Following receipt of the herpes zoster vaccine patients should wait an additional 4 to 6 weeks before resuming their biologic therapy.

**CONCLUSION**

Understanding the additional needs of the immunocompromised patient and encouraging them to receive the necessary vaccinations can be lifesaving. Inactive vaccines can be safely administered to immunocompromised patients, however, their needs are more complex and should be continually evaluated. The influenza vaccine should be administered yearly, while the pneumococcal, hepatitis A and B, HPV, Tdap and meningococcal vaccines should be administered after evaluation of patient specific risks and titer results. Solid organ transplant recipients should begin receiving vaccination 3 to 6 months following transplant, whereas HCT recipients should begin receiving vaccinations 6 months following transplant. The benefit of administering a live vaccine and the degree of immunosuppression must be carefully evaluated in the immunocompromised patient before this type of vaccine is administered, as in many cases it may be contraindicated. The herpes zoster vaccine should be given to patients ≥50 years with immune-mediated diseases who are on certain immunosuppressive medications, if the dose is not considered immunosuppressive. Alternatively, the herpes zoster vaccination can be administered to patients who take a medication break from their immunosuppressive regimen.

**REFERENCES**


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**Perampanel (Fycompa®): A Novel Anti-Epileptic Drug**

Jennifer Dunn, PharmD

Epilepsy affects approximately 2.8 million patients in the United States with an estimated annual cost of $15.5 billion. Approximately 30% of these patients still experience persistent seizures despite concurrent treatment with multiple antiepileptic drugs (AEDs). Patients who have failed two or more AEDs are considered to have drug-resistant epilepsy (DRE). DRE significantly affects patient’s quality of life and contributes to the burden of epilepsy-disabilities.

In the past two decades, multiple AEDs have been developed to change treatment of epilepsy through novel mechanisms of action. First generation AEDs, including phenobarbital, phenytoin, carbamazepine, and valproate generally have more side effects, require monitoring, and have greater potential for drug-drug interactions. The development of second generation AEDs was geared toward improving the burdens and unfavorable effects of first generation AEDs. Based on available literature, second generation AEDs, such as...
lamotrigine, topiramate, oxcarbazepine, and gabapentin, are no more effective than first generation AEDs, but are now used more often due to increased tolerability, reduced need for monitoring, and fewer potential interactions.6

Currently AEDs have mechanisms of action targeting multiple different receptors including voltage-dependent sodium channels, calcium currents, GABA activity, and other mixed mechanisms.6 Perampanel (Fycompa®, Eisai Company Ltd.) is a novel AED targeting α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors.7 Perampanel was approved by the FDA in October 2012 with an indication for adjunctive therapy for partial seizures. In addition, perampanel’s properties may allow for treatment in other disease states and phase III studies are ongoing to determine efficacy in diabetic neuropathy and post-herpetic neuralgia. Eisai Company is also researching perampanel in pediatric partial onset seizures and generalized seizures.8 Because of perampanel’s novel mechanism of action, this agent may play a significant role in the treatment of refractory epilepsy. The objectives of this article are to review pharmacology, pharmacokinetics, efficacy, and safety of perampanel, a new anti-epileptic drugs used as adjunctive treatment of partial onset seizures.

**Mechanism of Action**

Glutamate receptors, including AMPA, NMDA, and kainite, are the principal mediators of fast excitatory postsynaptic neurotransmission involved in epileptic activity.9,10 In epilepsy, AMPA-glutamate receptors spread seizure activity due to the increased hypersensitivity and quantity of glutamate binding sites.11 Perampanel is a highly selective, noncompetitive AMPA-type glutamate receptor antagonist, which decreases fast excitatory neurotransmission. Perampanel binds exclusively to the AMPA-glutamate receptors and does not affect other receptors.12

**Pharmacokinetics & Pharmacodynamics**

Perampanel has complete and rapid absorption and is highly protein bound and extensively metabolized through liver enzymes, primarily cytochrome P450 3A4 (CYP3A4) and 3A5 (CYP3A5).2 Perampanel has a half-life of approximately 105 hours, allowing for once daily dosing.2 Perampanel avoids unfavorable adverse effects that are present with other glutamate antagonists. Specifically, NMDA-glutamate type receptor antagonists have significant psychotomimetic effects leading to hallucinations, nightmares, and confusion. Potential drug interactions between perampanel and other AEDs are shown in Table 1. Excretion is primarily through the feces (48%) and urine (22%).7

**Drug Interactions**

Due to extensive metabolism by CYP3A4, drug interactions can occur between perampanel and strong inhibitors or inducers of CYP3A4, such that plasma levels may be decreased if given concurrently with CYP3A4 enzyme inducers and increased if given concurrently with CYP3A4 inhibitors.6 Based on the current evidence, perampanel may increase serum concentration of oxcarbazepine but does not affect serum concentration of all other AEDs.7,11

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Drugs</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP3A4 Inducers</strong></td>
<td>Carbamazepine, Phenobarbital, Phenytoin, Primidone</td>
<td>Decreased serum concentrations of perampanel</td>
</tr>
<tr>
<td>Mixed inhibitor/inducer</td>
<td>Oxcarbazepine</td>
<td>Decreased serum concentrations of perampanel or increase serum concentration of oxcarbazepine</td>
</tr>
</tbody>
</table>

**Editor’s Summary: Perampanel (Fycompa®)**

**Description & Indication**
- Selective, noncompetitive AMPA-type glutamate receptor antagonist; ↓ fast excitatory neurotransmission
- Approved as adjunct treatment of partial-onset seizures

**Dosing**
- 2-4 mg once at bedtime initially; dose not to exceed 12 mg/day (lower maximum doses in select patients – see Table 2)

**Efficacy**
- 8-12 mg/day effective in refractory partial-onset seizures in patients ≥12 years of age
- 12 mg/day is more effective in reducing seizure frequency, but at cost of increased adverse effects

**Safety**
- Generally well-tolerated; dizziness and somnolence the most common adverse effects & both are dose-dependent with higher incidences at higher doses
Dosing

The recommended daily dose of perampanel is 8-12 mg except in patients with hepatic impairment (Table 2). The initial dose is generally 2 mg daily unless being taken with drugs that induce CYP450 enzymes. The minimum effective dose is 4 mg/day, while the total daily dose should not exceed 12 mg. Perampanel is commercially available as 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets.

Efficacy in Clinical Trials

All three phase III studies of perampanel to date have evaluated efficacy and safety of perampanel as an adjunctive medication for treatment of refractory partial-onset seizures in patients 12 years and older (Table 3).10,11,14 Patients with partial seizures with or without motor signs, complex partial and complex partial with secondary generalization were enrolled in these studies. Patients were included if they had failed at least two AEDs in the previous two years and had experienced at least five partial seizures in the 6-week baseline phase. The primary endpoints were the same for each trial and included responder rate and the percent change in seizure frequency in the 4 weeks following initiation of perampanel. The responder rate was defined as the percent of patients who experienced ≥50% reduction in seizure frequency. Patient diaries were used to measure the efficacy of the primary endpoints. The Clinical and Patient Global Impression of Change (CGIC/PGIC) Questionnaire was also used as a measurement of efficacy but was not considered a primary or secondary endpoint. The questionnaire takes into account the patient’s history, psychosocial circumstances, symptoms, behavior, and impact of symptoms on the patient’s ability to function.15 All the trials looked at perampanel in addition to 1-3 antiepileptic drugs with uncontrolled partial-onset seizures including only one enzyme inducing AED (carbamazepine, phenytoin, phenobarbital, or primidone). The most common concomitant AEDs were levetiracetam, carbamazepine, lamotrigine, and valproic acid.

Study 304 assessed efficacy and safety of the 8 mg daily dose and 12 mg daily dose compared with placebo.10 Patient enrollment occurred in North America, Central America, and South America. The majority of patients (55.7%) were taking two other AEDs. The results of the primary outcome are summarized in Table 3. The secondary outcome evaluated percent change in seizure frequency per 28 days of complex partial seizures and secondarily generalized seizures after drug initiation. The percent reduction from baseline was 33.0% (p=0.0020) and 33.1% (p=0.0081) for 8 mg and 12 mg daily doses, respectively. Patients treated with 8 mg daily also reported significantly greater improvement on the CGIC compared with placebo-treated patients. Perampanel-treated patients, regardless of dose, did not have a significantly better score on the PGIC compared with placebo.10

Study 305 assessed efficacy and safety of the 8 mg daily dose and 12 mg daily dose compared with placebo.14 This study enrolled patients from the United States, many European countries, Russia, Australia, and South Africa. The most common seizure type was complex partial seizures (>80%) in both dosage groups. More than 50% of the patients were on 3 concomitant AEDs. The results of the primary outcome are summarized in Table 3. The secondary outcome evaluated percent change in seizure frequency per 28 days of complex partial seizures and secondarily generalized seizures after drug initiation. The percent reduction from baseline was 32.7% (p<0.001) and 21.9% (p=0.005) for 8 mg and 12 mg daily doses, respectively. Patients treated with perampanel 8 mg and 12 mg also reported significantly greater improvement on the CGIC compared with placebo-treated patients (p<0.05

Table 2 | Manufacturer-recommended perampanel dosing and titration schedule.7,13

<table>
<thead>
<tr>
<th>Dosing Group</th>
<th>Starting Dose</th>
<th>Titration Rate</th>
<th>Recommended Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical oining</td>
<td>2 mg QHS</td>
<td>Increase DD by 2 mg/week</td>
<td>8-12 mg</td>
</tr>
<tr>
<td>Presence of Enzyme-Inducing AEDs</td>
<td>4 mg QHS</td>
<td>Increase DD by 2 mg/week</td>
<td>8-12 mg</td>
</tr>
<tr>
<td>Hepatic Impairment</td>
<td>2 mg QHS</td>
<td>Increase DD by 2 mg every two weeks</td>
<td>Mild: 6 mg Moderate: 4 mg Severe: not recommended</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>2 mg QHS</td>
<td>Increase DD by 2 mg every two weeks</td>
<td>Mild-to-moderate: 8-12 mg Severe: not recommended</td>
</tr>
<tr>
<td>Elderly Patients</td>
<td>2 mg QHS</td>
<td>Increase DD by 2 mg every two weeks</td>
<td>8-12 mg</td>
</tr>
</tbody>
</table>

AEDs = anti-epileptic drugs; DD = daily dose; QHS = once daily at bedtime.
for both perampanel groups compared with placebo). Patients being treated with 8 mg daily also reported a significant improvement on the PGIC (p=0.021).

Study 306 assessed the dose response of the 2 mg, 4 mg, and 8 mg daily doses. Patients were enrolled from Germany, Bulgaria, Portugal, Lithuania, India, and China. The majority of patients (>80%) were taking 2 or 3 AEDs. Results of the primary outcome are summarized in Table 3. The main secondary outcome was percent change in seizure frequency per 28 days of complex partial plus secondarily generalized seizures. The percent reduction from baseline was 31.2% (p=0.007) and 38.7% (p<0.001) for 4 mg and 8 mg daily doses, respectively. The 2 mg daily dose did not show a statistically significant reduction in seizure reduction, therefore, 4 mg is considered the minimal effective dose.

### SAFETY

The most common adverse effects that led to discontinuation of perampanel in clinical trials were dizziness, somnolence, fatigue, and headache (Table 4). Other adverse effects that lead to discontinuation within the three different studies included: fall, irritability, weight increase, ataxia, upper respiratory tract infection, nasopharyngitis, and gait disturbances. All adverse effects seen in the studies were rated as mild-to-moderate in severity. Dizziness appeared to be a dose-related adverse effect. Perampanel has a black box warning of serious psychiatric and behavioral reactions. The behavioral reactions could include aggression, hostility, irritability, anger, and homicidal ideation. Patients should be monitored for mood changes, especially during the titration period.

### ROLE IN THERAPY

Currently, the existing AEDs work by effecting different types of neurotransmission. The majority of AEDs affect the voltage dependent sodium channels or GABA activity. Previously, the American Academy of Neurology/American Epilepsy Society (AAN/AES) recommended the use of lamotrigine, gabapentin, oxcarbazepine, or topiramate for treatment of refractory seizures. Topiramate has a mixed mechanism of action, including activity at glutamate receptors, and lamotrigine, oxcarbazepine, and gabapentin affect the sodium and calcium channels. In contrast, perampanel is very selective for AMPA-glutamate receptors. Based on recent efficacy studies and the unique mechanism of action perampanel may have a role in therapy for refractory seizures and drug-resistant epilepsy. However, the exact place in therapy for perampanel remains to be seen. Future studies will need to identify at what point perampanel should be prescribed and the most appropriate combinations of AED in which to include perampanel.

Current studies are evaluating perampanel for use in peripheral diabetic neuropathy and post-herpetic neuralgia. However, at present, perampanel does not have any FDA-approved indication for these conditions.

### Table 3 | Perampanel efficacy studies in patients with partial refractory seizures.10,11,14

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Primary Endpoints</th>
<th>Median % Change in Seizure Frequency</th>
<th>Responder Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 304 (2012)</td>
<td>PER 8 mg (n=133)</td>
<td>% change in seizure frequency</td>
<td>PER 8 mg: -26.3% (p=0.026)</td>
<td>PER 8 mg: 37.6% (p=NS)</td>
</tr>
<tr>
<td></td>
<td>PER 12 mg (n=134)</td>
<td>Responder rate</td>
<td>PER 12 mg: -34.5% (p=0.016)</td>
<td>PER 12 mg: 36.1% (p=NS)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=121)</td>
<td>placebo</td>
<td>Placebo: -21.0%</td>
<td>Placebo: 26.4%</td>
</tr>
<tr>
<td>Study 305 (2013)</td>
<td>PER 8 mg (n=129)</td>
<td>% change in seizure frequency per 28 days relative to baseline</td>
<td>PER 8 mg: -30.5% (p&lt;0.001)</td>
<td>PER 8 mg: 33.3% (p=0.002)</td>
</tr>
<tr>
<td></td>
<td>PER 12 mg (n=121)</td>
<td>Responder rate</td>
<td>PER 12 mg: -17.6% (p=0.01)</td>
<td>PER 12 mg: 33.9% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=136)</td>
<td>placebo</td>
<td>Placebo: -9.7%</td>
<td>Placebo: 14.7%</td>
</tr>
<tr>
<td>Study 306 (2012)</td>
<td>PER 2 mg (n=180)</td>
<td>% change in seizure frequency per 28 days</td>
<td>PER 2 mg: -13.6% (p=NS)</td>
<td>PER 2 mg: 20.6% (p=NS)</td>
</tr>
<tr>
<td></td>
<td>PER 4 mg (n=172)</td>
<td>Responder rate</td>
<td>PER 4 mg: -23.3% (p=NS)</td>
<td>PER 4 mg: 28.5% (p=0.013)</td>
</tr>
<tr>
<td></td>
<td>PER 8 mg (n=169)</td>
<td>placebo</td>
<td>PER 8 mg: -30.8% (p&lt;0.001)</td>
<td>PER 8 mg: 35.9% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=185)</td>
<td>placebo</td>
<td>Placebo: -10.7%</td>
<td>Placebo: 17.9%</td>
</tr>
</tbody>
</table>

NS = not statistically significant.
Perampanel is a newly approved antiepileptic drug for the management of refractory partial-onset seizure. In contrast to other AEDs, perampanel inhibits the AMPA-glutamate type receptors. Studies have shown that perampanel in doses of 8 or 12 mg are effective at reducing the percentage of seizure in a 28 day period as well as reducing the rate of seizures for patients by more than 50% from baseline. It has been approved as an adjunctive AED for patients and may be appropriate for patients that have failed other first line AEDs. A major limitation of perampanel is potential drug-drug interactions with enzyme-inducing medications that are commonly used in epilepsy resulting in decreased serum concentrations of perampanel. Perampanel is currently only available in Europe; the timeline for availability in the U.S. is currently unknown.

**CONCLUSION**

Perampanel is a newly approved antiepileptic drug for the management of refractory partial-onset seizure. In contrast to other AEDs, perampanel inhibits the AMPA-glutamate type receptors. Studies have shown that perampanel in doses of 8 or 12 mg are effective at reducing the percentage of seizure in a 28 day period as well as reducing the rate of seizures for patients by more than 50% from baseline. It has been approved as an adjunctive AED for patients and may be appropriate for patients that have failed other first line AEDs. A major limitation of perampanel is potential drug-drug interactions with enzyme-inducing medications that are commonly used in epilepsy resulting in decreased serum concentrations of perampanel. Perampanel is currently only available in Europe; the timeline for availability in the U.S. is currently unknown.

**REFERENCES**


**Table 4 | Treatment emergent adverse effects in ≥10% of patients in clinical trials.**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Study 304 ‡ ‡</th>
<th>Study 305 ‡ ‡</th>
<th>Study 306 ‡ ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>10% 38% 38%</td>
<td>7% 33% 48%</td>
<td>10% 10% 17%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13% 18% 17%</td>
<td>3% 12% 18%</td>
<td>7% 12% 9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>n/a n/a n/a</td>
<td>8% 13% 17%</td>
<td>3% 4% 7%</td>
</tr>
<tr>
<td>Headache</td>
<td>13% 15% 13%</td>
<td>13% 9% 4%</td>
<td>9% 9% 5%</td>
</tr>
</tbody>
</table>

n/a = data not available.

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