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Introduction
Brexpiprazole (Rexulti®) was approved by the Food and Drug Administration (FDA) on July 10, 2015 for the treatment of schizophrenia and adjunct therapy for major depressive disorder (MDD) in adults. Further studies are being conducted for brexpiprazole’s efficacy in post-traumatic stress disorder (PTSD) and agitation in Alzheimer’s disease (AD), which are both novel indications for any atypical antipsychotic.
Compared to its predecessor molecule aripiprazole, brexpiprazole shares structural characteristics and binding profiles. Brexpiprazole is a partial agonist for serotonin type 1A (5-HT$_{1A}$) and dopamine type 2 (D$_2$) receptors and acts as an antagonist at serotonin type 2A (5-HT$_{2A}$) receptors. Pharmacologic studies demonstrate higher binding affinities of brexpiprazole for the 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors compared to D$_2$ receptors, which allows for antipsychotic and other central nervous system (CNS) activity without significant dopamine-associated adverse effects commonly observed with other antipsychotic treatments. At this time, no head-to-head trials have been identified directly comparing brexpiprazole to other antipsychotics, but it is believed that there will be a lower incidence of metabolic disorders, extrapyramidal symptoms (EPS), and tardive dyskinesia associated with brexpiprazole.

**Efficacy**

The efficacy and safety of brexpiprazole were evaluated in 2 phase III trials for schizophrenia (BEACON and VECTOR) and 2 phase III trials for MDD (Polaris and Pyxis). These trials are outlined in Table 1.

**Schizophrenia**

BEACON and VECTOR trials are randomized, double-blind, placebo-controlled, multicenter studies in patients with a Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) diagnosis of schizophrenia and experiencing acute exacerbation of psychotic symptoms at the time of enrollment. An acute exacerbation of symptoms was defined as deterioration from usual functioning, a total Brief Psychiatric Rating Scale (BPRS) score $\geq 40$, a score of $\geq 4$ on 2 or more BPRS items (hallucinatory behavior, unusual thought content, conceptual disorganization, or suspiciousness), and Clinical Global Impressions-Severity Scale (CGI-S) score $\geq 4$. Patients were also included if they were thought to benefit from hospitalization. The primary endpoint for both trials was change from baseline at 6 weeks in Positive and Negative Syndrome Scale (PANSS, a 30-item scale, score range 30 [best] to 210 [worst]).

The BEACON trial recruited 674 patients and evaluated brexpiprazole doses 1 mg, 2 mg, and 4 mg, administered once-daily, compared to placebo. Current use of other antipsychotics, antidepressants, mood stabilizers, or benzodiazepines was prohibited. Investigators observed a statistically significant reduction in PANSS scores at week 6 in patients receiving brexpiprazole 4 mg compared to placebo (mean difference: -6.47, p=0.0022); reductions were also observed with brexpiprazole 2 mg and 1 mg but the differences were not statistically significant (-3.08, p=0.1448; and -3.37, p=0.1588 respectively). There were no adverse effects reported frequently ($\geq 5\%$ in brexpiprazole groups, or $\geq 2$ times the placebo rate) and there were no laboratory changes in any group. Akathisia was reported less frequently in the brexpiprazole groups compared to placebo, but moderate weight gain was observed more with brexpiprazole use. The trial demonstrated clinically meaningful improvements in baseline PANSS scores after 6 weeks of therapy with brexpiprazole 4 mg daily compared to placebo.

In the VECTOR trial, 623 patients were randomized to brexpiprazole (0.25 mg, 2 mg, or 4 mg daily) or placebo. Greater reductions in PANSS scores were observed with brexpiprazole 4 mg (mean difference: -7.64, p=0.0006) and 2 mg (mean difference: -8.72, p<0.0001) compared to placebo; minimal differences were observed between brexpiprazole 0.25 mg and placebo (mean difference: -2.89, p=0.30). The incidence of adverse effects was greater in the placebo group compared to the treatment groups (62.0% vs. 48.9-56.7%, respectively) and differences in metabolic and laboratory measures between treatment and placebo were not
clinically or statistically significant. Akathisia was reported more frequently in brexpiprazole 2 mg and 4 mg groups compared to placebo, but study investigators reported the severity as mild or moderate. Increased body weight was observed more frequently in the brexpiprazole 2 mg and 4 mg groups compared to placebo (mean change at 6 weeks: 1.45 kg, 1.28 kg and 0.42 kg, respectively). Study authors concluded 2 mg or 4 mg of brexpiprazole daily was safe and effective in reducing PANSS scores compared to placebo, with statistically significant improvements noticed within 1-2 weeks of therapy.

Table 1. Summary of brexpiprazole phase III clinical trials.4-9

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design and duration</th>
<th>Enrollment</th>
<th>Treatment groups</th>
<th>Mean change in PANSS total score at 6 weeks*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEACON</td>
<td>R, DB, PC, MC</td>
<td>n=674 patients, aged 18 to 65 years with schizophrenia</td>
<td>Brexpiprazole: • 1 mg daily (n=81) • 2 mg daily (n=129) • 4 mg daily (n=130) Placebo (n=118)</td>
<td>1 mg: -16.90 (p=0.1588) 2 mg: -16.61 (p=0.1448) 4 mg: -20.00 (p=0.0022) Placebo: -13.53</td>
</tr>
<tr>
<td>VECTOR</td>
<td>R, DB, PC, MC</td>
<td>n=623 patients, aged 18 to 65 years with schizophrenia</td>
<td>Brexpiprazole: • 0.25 mg daily (n=87) • 2 mg daily (n=180) • 4 mg daily (n=178) Placebo (n=178)</td>
<td>0.25 mg: -14.90 (p=0.30) 2 mg: -20.73 (p&lt;0.0001) 4 mg: -19.65 (p=0.0006) Placebo: -12.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design and duration</th>
<th>Enrollment</th>
<th>Treatment groups</th>
<th>Mean change in PANSS total score at 6 weeks*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyxis</td>
<td>R, DB, PC, MC, FD</td>
<td>n=379 patients aged 18 to 65 years with MDD</td>
<td>Brexpiprazole: • 2 mg daily (n=175) Placebo (n=178) **Background ADT</td>
<td>+2 mg: -8.36 (p=0.0002) +Placebo: -5.15</td>
</tr>
<tr>
<td>Polaris</td>
<td>R, DB, PC, MC, FD</td>
<td>n=677 patients aged 18 to 65 years with MDD</td>
<td>Brexpiprazole: • 1 mg daily (n=226) • 3 mg daily (n=230) Placebo (n=221) **Background ADT</td>
<td>+1 mg: -7.64 (p=0.0737) +3 mg: -8.29 (p=0.0079) +Placebo: -6.33</td>
</tr>
</tbody>
</table>

ADT=approved antidepressant therapy; DB=double blind; FD=fixed dose; MADRS=Montgomery-Asberg Depression Rating Scale; MC=multicenter; MDD=major depressive disorder; PANSS=Positive and Negative Syndrome Scale; PC=placebo controlled; R=randomized
*P-values reported for comparisons to placebo
**All patients in Pyxis and Polaris received treatment or placebo in combination with ADT

MDD

Pyxis and Polaris are randomized, double-blind, fixed-dose, placebo-controlled trials that evaluated the efficacy of brexpiprazole as adjunctive therapy to FDA-approved antidepressant treatment (ADT). Approved ADT therapies were escitalopram (10 mg or 20 mg/day), fluoxetine (20 mg or 40 mg/day), paroxetine controlled-release (CR, 37.5 mg or 50 mg/day), sertraline (100 mg, 150 mg, or 200 mg/day), duloxetine (40 mg or 60 mg/day), or venlafaxine extended-release (XR 75 mg, 150 mg, 225 mg/day). Prior to the initiation of brexpiprazole, patients received ADT for 8 weeks, and ADT was titrated to the maximum tolerated dose to account for optimization of therapy. Patients were only included if they had an inadequate response to ADT therapy, defined as Hamilton Depression Rating Scale 17-item (HDRS-17) score ≥14, <50% reduction of...
HDRS-17 and Montgomery-Asberg Depression Rating Scale (MADRS) total score between start of prospective treatment and each scheduled visit, and Clinical Global Impressions-Improvement scale (CGI-I) score ≥3. The primary end point and efficacy measure for both trials was mean change from baseline at 6 weeks in MADRS (a 10-item clinician-rated scale, score range: 0 [no symptoms] to 60 [worst symptoms]).

The Pyxis trial included 379 patients, with 175 patients assigned to receive brexpiprazole 2 mg/day or placebo. Patients receiving brexpiprazole had a greater mean reduction in MADRS total score compared to those on placebo, with differences observed as early as week 1. The most common adverse effects for brexpiprazole were weight gain (8.0%) and akathisia (7.4%), which the study investigators reported as mild-to-moderate (mean increase of 1.64 kg at week 6, and small increases in EPS rating scales compared to placebo). There were no significant differences between brexpiprazole and placebo in restlessness, insomnia, anxiety, fatigue, fasting glucose, fasting lipid panel, vital signs, and electrocardiogram changes. Brexpiprazole 2 mg/day was found to be safe and efficacious as adjunct therapy for MDD.

The Polaris trial enrolled 677 participants who were randomized 1:1:1 to receive ADT with brexpiprazole 1 mg/day, 3 mg/day, or placebo. Greater improvements in total MADRS scores were observed with brexpiprazole 3 mg compared to placebo (-8.29 vs. -6.33 respectively, p=0.0079), and brexpiprazole 1 mg also showed improvement in mean total MADRS score compared to placebo (-7.64 vs. -6.33, p=0.0737), but this finding was not statistically significant. The most common adverse effects (>5%) reported in the brexpiprazole 1 mg group were headache, nasopharyngitis, and weight gain; common adverse effects in the brexpiprazole 3 mg group were akathisia, headache, somnolence, weight gain, and tremor. Most of the treatment-associated adverse effects were noted as mild-to-moderate by study investigators. Changes in mean body weight for both treatment groups were not significantly different compared to placebo (p<0.0001). EPS was reported more frequently with brexpiprazole 3 mg compared to placebo, with akathisia (13.5% vs. 2.3%) and tremor (5.2% vs. 3.2%) having the highest reported incidence. Overall, activating adverse effects (restlessness, anxiety, and insomnia) were infrequently reported. There were no significant, clinically relevant changes in metabolic values for all groups. In summary, addition of brexpiprazole 3 mg to ADT improved depressive symptoms as determined by MADRS scores in patients with inadequate response to ADT alone.

Due to the lack of head-to-head trials, it is uncertain how brexpiprazole compares to other atypical antipsychotics currently approved for schizophrenia and MDD (aripiprazole, quetiapine, and olanzapine-fluoxetine combination). There are 2 ongoing trials evaluating the efficacy of brexpiprazole compared to aripiprazole (NCT02054702) and quetiapine XR (NCT01810380); further conclusions may be drawn following their completion.

Safety

Boxed warnings

Brexpiprazole carries 2 boxed warnings: increased risk of suicidality in children and young adults and increased risk of death in elderly patients with dementia-related psychosis. Notably, the former warning applies to all FDA-approved antidepressant agents, and the latter warning applies to all atypical antipsychotics. Patients should be closely monitored during initiation of treatment and during dose changes for clinical worsening. Currently, the safety and efficacy of brexpiprazole have not been established in pediatric patients, but young
adults (ages 18-24) should still be closely observed. Use of brexpiprazole in geriatric patients has been reported to be safe based on data from safety, tolerability, and pharmacokinetic studies.

**Adverse reactions**

Long term therapy adherence is crucial to maintain disease remission and remain symptom free, especially with schizophrenia, and having a proposed smaller side effect profile compared to other available agents increases the likelihood of adherence.\(^1\),\(^2\),\(^6\),\(^12\) Available data suggest minimal metabolic adverse effects, weight gain, and EPS with brexpiprazole compared to placebo.\(^4\),\(^7\)-\(^9\) Although there are no active-controlled trials, the pharmacologic profile of brexpiprazole (i.e., involving high binding affinity to neurotransmitter receptors compared to other antipsychotics) suggests a potential for decreased adverse effects.\(^1\),\(^2\),\(^9\) Results from placebo-controlled trials suggest lower frequencies of akathisia (vs. aripiprazole), increased appetite and weight gain (vs. olanzapine), and sedation and somnolence (vs. quetiapine).\(^3\),\(^8\) Relative adverse effects of brexpiprazole and other second generation antipsychotics may be seen in Table 2. Data from head-to-head trials are necessary to more accurately assess the comparative safety of these agents.

**Drug interactions**

Brexpiprazole is primarily metabolized by cytochrome P450 (CYP) 3A4 and CYP2D6; moderate and strong enzyme inducers and inhibitors can affect the concentration of brexpiprazole.\(^12\) It is recommended to reduce brexpiprazole dose by 50% if used with a strong CYP3A4 or CYP2D6 inhibitor, reduce the dose by 25% if used with moderate CYP3A4 and CYP2D6 inhibitors together, or, if the patient is taking a strong CYP3A4 or CYP2D6 inducer, gradually double the brexpiprazole dose over 1-2 weeks. There is a potential for the development of serotonin syndrome if used concurrently with other serotonergic agents due to brexpiprazole’s activity on 5-HT\(_{1A}\) and 5-HT\(_{2A}\).

**Dosage and administration**

For the treatment of schizophrenia, the manufacturer recommends initiating brexpiprazole at a dose of 1 mg daily, titrated to a daily dose of 2 to 4 mg.\(^12\) The maximum daily dose is 4 mg. For MDD, the manufacturer recommends an initial dose of 0.5 or 1 mg daily, titrated to 2 mg daily; the maximum daily dose is 3 mg. If a patient has hepatic impairment with a Child-Pugh score of 7 or greater or renal impairment with creatinine clearance <60 mL/min, the maximum daily dose is 3 mg for schizophrenia and 2 mg for MDD.

**Place in treatment**

Brexpiprazole is deemed efficacious in the treatment of schizophrenia and as adjunct therapy for MDD, like many other atypical antipsychotics.\(^3\)-\(^5\),\(^7\)-\(^9\),\(^13\) At present, the lack of head-to-head trials comparing brexpiprazole to other atypical antipsychotics makes it difficult to determine if brexpiprazole is more efficacious or better tolerated. Comparisons using currently available trials may not be reliable due to their heterogeneity.\(^4\),\(^7\)-\(^9\) Of note, the aforementioned phase III trials evaluating brexpiprazole were of 6 weeks’ duration, precluding any assertions on its long-term efficacy and safety. A longer duration of medication therapy is typically required, especially for treatment of schizophrenia.\(^3\),\(^13\)
Additional trials are underway to determine efficacy and tolerability of brexpiprazole in patients with moderate-to-severe AD with clinically significant agitation.\(^3,13\) The double-blind, placebo-controlled trials are assessing the efficacy (NCT01862640) and safety (NCT01922258) of brexpiprazole 1 mg daily and brexpiprazole 2 mg daily.\(^14,15\) Investigators of a randomized, double-blind, placebo-controlled trial are in the process of recruiting patients to evaluate the efficacy of brexpiprazole as adjunctive treatment to paroxetine or sertraline for PTSD symptoms (NCT01987960).\(^16\) If the study demonstrates positive results, brexpiprazole would be the first antipsychotic approved for PTSD. Currently, sertraline and paroxetine are the only FDA-approved medications for treatment of PTSD; all other treatments are used off-label, and the evidence for their efficacy is inconclusive.

### Table 2. Relative adverse effects of second generation antipsychotics\(^3,13\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Diabetes</th>
<th>Weight gain</th>
<th>EPS</th>
<th>QTc prolongation</th>
<th>Hyper-prolactinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Asenapine</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Clozapine</td>
<td>++++</td>
<td>++++</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>++++</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>+++</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

EPS=extrapyramidal symptoms

### Conclusion

Brexpiprazole is a newly-approved atypical antipsychotic for the treatment of schizophrenia and adjunctive therapy for MDD. Potential advantages include a favorable side effect profile and novel uses. Results from ongoing studies may provide more information and allow for additional recommendations on brexpiprazole therapy. As always, selection of an agent for treatment of psychiatric conditions should be individualized for each patient.

### References


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**Tdap Recap – An Update on the Role of Pharmacists as Immunizers**

*Marisa Censi, PharmD*

**Introduction**

On July 1, 2015, an amendment expanding immunization scope of practice for pharmacists in New York State (NYS) went into effect.¹,² This revision enables pharmacists to administer vaccinations to protect against tetanus, diphtheria, and pertussis pursuant to a patient specific or non-patient specific order. It also authorizes pharmacists to administer vaccines protecting against herpes zoster and meningitis pursuant to a non-patient specific order. The bill was first introduced in response to an increase in cases of pertussis among patients in NYS. There has been a recent upward trend in pertussis outbreaks throughout the country.³,⁴ Rates of pertussis decreased after the 1940s, following the first recommendations to routinely vaccinate children against pertussis. Rates began to rise drastically around 2002, reaching a peak in 2012 of 48,277 cases reported to the Centers for Disease Control and Prevention (CDC).
Disease overview

Pertussis, also known as whooping cough, is a respiratory illness caused by the bacterium *Bordatella pertussis*. Pertussis is highly contagious and is spread via droplet transmission. The illness is most dangerous for infants and young children; they are more prone to serious complications, including apnea, pneumonia, convulsions, encephalopathy, and death. Symptoms typically present 5-10 days after exposure and progress through 3 stages, described in Figure 1. About half of infants with pertussis are hospitalized for treatment, while only about 5% of teens and adults are hospitalized. Immunization with the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine is an effective way to prevent contraction of the disease, and more importantly, to prevent the spread of the disease. If pertussis is contracted in patients who have been vaccinated, symptoms are typically milder and without the characteristic “whooping” sound.

**Figure 1. Stages of pertussis.**

**Stage 1: Catarrhal Stage**
Cold-like symptoms, such as runny nose, mild cough, low-grade fever, and apnea (in infants)
Duration: 1-2 weeks

**Stage 2: Paroxysmal Stage**
Violent coughing fits, also known as paroxysms, causing the signature “whoop” sound, and can result in vomiting and extreme fatigue
Duration: 1-6 weeks, up to 10 weeks

**Stage 3: Convalescent Stage**
Coughing lessens and patients begin to recover, but are still susceptible to other respiratory illnesses
Duration: 2-3 weeks

Current vaccination recommendations

The CDC’s Advisory Committee for Immunization Practices (ACIP) provides the most widely accepted recommendations for vaccinations, including the Tdap vaccine. ACIP recommendations for the Tdap vaccine are summarized in Table 1.

Vaccine dosing and administration

Two manufacturers produce Tdap vaccines in the United States: Sanofi Pasteur as Adacel® and GlaxoSmithKline as Boostrix®. Both products are available as single-dose vials and prefilled syringes.
containing 0.5 mL suspension for injection. The vaccine should be stored in the refrigerator (2-8°C or 35-46°F) prior to use and should not be frozen. To prepare for injection, the vial or syringe should be shaken vigorously to produce a white, cloudy suspension and inspected for discoloration and particulates. The vaccine should be given as a single 0.5 mL dose administered intramuscularly into the deltoid muscle.

### Table 1. Summary of recommendations for the Tdap vaccine.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>- For children who did not receive the full childhood vaccination series for pertussis, one dose of Tdap is recommended</td>
</tr>
<tr>
<td>Age: 7-10 years</td>
<td>- For those children who were never vaccinated against tetanus, diphtheria, or pertussis, or for those whose vaccination history is not known, 1 dose of Tdap should be given, followed by a series of 2 additional doses of vaccinations with tetanus and diphtheria toxoids</td>
</tr>
<tr>
<td>Adolescents</td>
<td>- One dose of Tdap is recommended in place of a Td booster dose in those adolescents who have completed the childhood series of tetanus, diphtheria, and pertussis vaccinations but have not received Td or Tdap</td>
</tr>
<tr>
<td>Age: 11-18 years</td>
<td>- The Tdap dose should ideally be administered at 11 or 12 years of age</td>
</tr>
<tr>
<td>Age: 19-64 years</td>
<td>- One dose of Tdap is recommended in place of a booster Td dose in those who have not previously received the Tdap vaccine</td>
</tr>
<tr>
<td>Age: ≥65 years</td>
<td>- One dose of Tdap is recommended in place of a booster Td dose in those that have not been previously vaccinated with the Tdap vaccine</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>- Although only 1 Tdap product is approved for use in this population (Boostrix®), the ACIP endorses use of either product</td>
</tr>
<tr>
<td>Age: ≥65 years</td>
<td>- One dose of Tdap is recommended with each pregnancy, regardless of previous Tdap vaccination</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>- It is preferred for the vaccine to be given during pregnancy (best timing is between 27 and 36 weeks gestation), but may be given immediately postpartum, if necessary</td>
</tr>
<tr>
<td>Contact with infants ≤12 months old</td>
<td>- One dose of Tdap is recommended, preferably at least 2 weeks prior to contact, to prevent transmission to the infant</td>
</tr>
<tr>
<td></td>
<td>- This includes healthcare professionals and childcare workers among others</td>
</tr>
</tbody>
</table>

ACIP=Advisory Committee for Immunization Practices; HICPAC=Healthcare Infection Control Practices Advisory Committee; Td=diphtheria toxoid; Tdap=tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis  
*There is no restriction on the spacing between doses of Tdap and Td

The Vaccine Information Statement should be supplied to every patient before administering the vaccine. The immunizer should be sure to screen for contraindications, inform the patient about risks and benefits of the vaccine, and report any adverse events to the patient’s healthcare provider and/or the Vaccine Adverse Event Reporting System (VAERS). Contraindications specific to the Tdap vaccine include hypersensitivity to any component of the vaccine and history of encephalopathy within the 7 days following a previous pertussis vaccine not attributable to another cause. The tip caps of the prefilled syringes of both products may contain latex, but the vial stopper does not contain latex. The Boostrix® vaccine is pregnancy category B; the Adacel® vaccine is pregnancy category C (see ACIP recommendations for pregnancy in Table 1). Reported adverse events include local injection site reactions, such as pain, swelling, or redness at the injection site, headache, fatigue, and gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain), among others.
Conclusion

As NYS law allows pharmacists to continue to grow as resources and advocates for immunizations, it is important for those in the profession to stay current regarding immunization schedules and guideline recommendations. This expansion to include the Tdap vaccine in the list of immunizations that may be administered by pharmacists is an instrumental advancement in the fight against pertussis.\(^1\)\(^2\) Many pharmacists have increased access to patients and can identify patients who need the vaccine. Pharmacists and other healthcare providers should work together to prevent pertussis outbreaks by increasing immunization rates with the Tdap vaccine.

References

Is Solanezumab the Answer in the Treatment for Alzheimer’s Disease?

Amanda Pinski, PharmD

Introduction

Alzheimer’s disease (AD) is a neurodegenerative disorder marked by decline in cognitive function. It is typically progressive and age-related, primarily associated with the elderly.1 AD is characterized by an accumulation of aggregated amyloid-beta (Aβ) peptide in the cerebral cortex and hippocampus and can be detected prior to the development of clinical symptoms.2,3 Current treatment modalities do not treat this accumulation.2 Cholinesterase inhibitors are agents that prevent the breakdown of acetylcholine in the brain; they can be used to treat mild-to-moderate or moderate-to-severe AD.2 Medications in this class include donepezil, rivastigmine, and galantamine. Donepezil and rivastigmine (patch) are indicated for treatment of mild, moderate, or severe AD.4,5 Galantamine is indicated for the treatment of mild-to-moderate AD.6 Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, regulates the activity of glutamate in the brain and is approved for moderate-to-severe AD.7 Additional medications targeting biomarkers have been studied for the treatment of AD. Solanezumab is an investigational humanized monoclonal antibody that preferentially binds to soluble forms of amyloid; it has been shown to promote clearance from the brain in pre-clinical studies.1,3,8 Solanezumab is an IgG1 antiamyloid monoclonal antibody, binding to the mid-domain of the Aβ peptide. To date, the efficacy and safety of solanezumab have been evaluated in 2 phase 3 trials, EXPEDITION 1 and 2, and an extension study, EXPEDITION-EXT. Findings from the delayed-start EXPEDITION-EXT trial have recently been published, generating media attention. EXPEDITION-EXT will be reviewed in this article. In order to understand the results, the original trials, EXPEDITION 1 and 2, must also be reviewed. Notably, additional trials are underway. EXPEDITION 3 is an ongoing phase 3 trial evaluating the safety and efficacy of solanezumab in patients with mild AD; results from this trial are not currently available.

Study designs

The designs for EXPEDITION 1 and 2 and the extension study are outlined in Figure 1 and described below.

EXPEDITION 1 and EXPEDITION 2

Doody et al reported the results of 2 phase 3 trials of solanezumab in the treatment of patients with mild-to-moderate AD.3 Both were double-blind, placebo-controlled trials that included patients aged >55 years with mild-to-moderate AD, without depression. Mild-to-moderate AD was defined as a score of 16 to 26 on the Mini-Mental Status Exam (MMSE) or by the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association, including the presence of amyloid plaques, neurofibrillary tangles, and lost connections between neurons. Solanezumab (400 mg) and placebo were administered as an intravenous infusion of approximately 70 mL over 30 minutes, once every 4 weeks for 18 months (80 weeks).
EXPEDITION-EXT

EXPEDITION-EXT was an open-label extension of EXPEDITION 1 and 2, in which participants with mild AD from both studies were maintained on solanezumab for up to 184 weeks. Patients with mild AD who received solanezumab in the previous trials were considered early-start while those who received placebo during these trials were considered delayed-start; these patients were switched to solanezumab following completion of EXPEDITION 1 or 2.\(^1\) Both groups continued treatment through week 184. The dosing and frequency of the solanezumab and placebo were the same for all trials.\(^1,3\) All patients remained blinded to the initial treatment arm. Approximately 58.2% of delayed-start patients and 61.0% of the early-start patients completed the 2-year extension (weeks 81-184).\(^1\)

Figure 1. EXPEDITION trial designs.\(^1,3,8\)

**EXPEDITION 1**
- Week 1 to 80
- Solanezumab vs. placebo
- n=1,012 randomized
- Mild AD: n=675
- Moderate AD: n=333

**EXPEDITION 2**
- Week 1 to 80
- Solanezumab vs. placebo
- n=1,040 randomized
- Mild AD: n=647
- Moderate AD: n=390

**EXPEDITION-EXT**
- Week 1 to 184
- Early-start (initial solanezumab): n=659
- Delayed-start (initial placebo): n=663

**Pooled mild AD population**
- n=1,322 randomized

Efficacy

**EXPEDITION 1 and EXPEDITION 2**

Primary outcomes were the changes from baseline to week 80 in the 11-item cognitive subscale of the AD Assessment scale (ADCS-cog11) score, with higher scores indicating greater cognitive impairment, and AD Cooperative Study-Activities of Daily Living scale (ADCS-ADL), with lower scores indicating worse functioning.\(^3\) After statistical analysis of EXPEDITION 1, the primary outcome for EXPEDITION 2 was revised to the change in scores on the 14-item cognitive subscale of the Alzheimer’s Disease Assessment scale.
(ASCs-cog14), although ADAS-cog11 and ADAS-cog14 were measured for both EXPEDITION 1 and EXPEDITION 2.

EXPEDITION 1 and EXPEDITION 2 did not show statistically significant differences in ADAS-cog14 scores in patients receiving solanezumab over placebo.\textsuperscript{3} Differences between the solanezumab group and the placebo group in change from baseline to week 80 for ADAS-cog11, ADAS-cog 14, and ADCS-ADL can be seen in Table 1. The results for ADAS-cog11 and ADCS-ADL scores in EXPEDITION 1 and 2 also did not show statistically significant differences regarding efficacy of solanezumab.

Siemers et al reviewed the results for secondary outcomes in patients with mild AD from the pooled EXPEDITION 1 and EXPEDITION 2 trials, including efficacy, biomarker and safety endpoints.\textsuperscript{8} In patients with mild AD, they observed less cognitive and functional decline favoring solanezumab, as measured by the ADAScog-14 and ADAScog-11. There were no significant differences from baseline to study completion in those receiving solanezumab compared to placebo in outcomes measured by ACDS-ADL (p=0.057), basic items of the ACDS-ADL (ADCS-bADL, p=0.24), and Clinical Dementia Rating Sum Boxes (CDR-SB, p=0.34). Pooled data from EXPEDITION 1 and EXPEDITION 2 revealed significant differences between the solanezumab and placebo groups with mild AD in ADAS-cog 11 and ADAS-cog14, both with p<0.05. These differences were observed from week 40 through week 80.

**EXPEDITION-EXT**

Efficacy measures included ASCS-cog14 (shown in Table 1) and ADCS-iADL, CDR-SB, MMSE, ASCS-cog11, and ADCS-bADL.\textsuperscript{1} Non-inferiority tests were performed by developing a 90\% one-sided confidence interval, requiring a lower limit greater than 0 to demonstrate non-inferiority. Superiority analyses were also performed with a 2-sided p-value of ≤0.05 using the same model for the non-inferiority analysis.

Treatment differences between groups at 108 weeks were similar to differences seen at the end of the placebo-controlled period in ADAS-cog14 and ADCS-iADL.\textsuperscript{1} Treatment differences in cognition and function at the end of the placebo-controlled period were preserved at week 108 within the predefined settings. The differences in ADAS-cog14 and ADCS-iADL, along with the differences in MMSE, increased steadily through the placebo-controlled period and remained stable throughout the extension period. Treatment differences for the CDR-SB were small during the placebo-controlled period but increased during the delayed-start period, with statistical significance reached at week 184 and non-inferiority met at multiple time points throughout the trial. Similarly, there were treatment differences in MMSE over the delayed-start period reaching significance at weeks 132 and 160; however, these findings did not meet criteria for non-inferiority at any time point. Results for the ADAS-cog11 were consistent with the ADAS-cog14 findings, and results for ADCS-bADL were similar to those of the CDR-SB: no statistically significant differences were observed between solanezumab and placebo, but significant changes were observed during the extension study.

**Safety**

Regarding safety in the mild-to-moderate AD population, EXPEDITION 1 and EXPEDITION 2 found that there were no statistically significant differences in adverse events between patients in the solanezumab and placebo groups.\textsuperscript{3} There were also no adverse events where the rate in the solanezumab groups was twice the rate of the adverse event in the placebo groups.\textsuperscript{8} The EXPEDITION-EXT trial encompasses data for the mild AD
population for both the EXPEDITION 1 and 2 trials. Adverse events did not differ significantly between the solanezumab and placebo groups or in the early-start versus the delayed-start groups. All adverse events occurred with similar rates across both placebo and treatment groups. There were no treatment-related adverse events. The most notable adverse events included cardiac events, as well as amyloid-related imaging abnormalities with edema or hemorrhage, which has been associated with anti-amyloid treatments. These adverse events are shown in Table 2.

Table 1. Summary of primary efficacy measures in EXPEDITION 1, EXPEDITION 2, and EXPEDITION-EXT trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design and duration</th>
<th>Enrollment</th>
<th>Outcomes, by AD severity: difference in mean change from baseline to study completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solanezumab vs. placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXPEDITION 1&lt;sup&gt;3&lt;/sup&gt;</td>
<td>R, DB</td>
<td>n=1012, mild-to-moderate AD</td>
<td>Overall:</td>
</tr>
<tr>
<td></td>
<td>80 weeks</td>
<td></td>
<td>- ADAS-cog11: -0.8 (95% CI: -2.1 to 0.5, p= 0.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ADAS-cog14: -1.4 (95% CI: -2.9 to 0.2, p= 0.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ADCS-ADL: -0.4 (95% CI: -2.3 to 1.4, p= 0.64)</td>
</tr>
<tr>
<td>EXPEDITION 2&lt;sup&gt;3&lt;/sup&gt;</td>
<td>R, DB</td>
<td>n=1040, mild-to-moderate AD</td>
<td>Overall:</td>
</tr>
<tr>
<td></td>
<td>80 weeks</td>
<td></td>
<td>- ADAS-cog11: -1.3 (95% CI: -2.5 to 0.3, p= 0.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ADAS-cog14: -1.6 (95% CI: -3.1 to 0.1, p=0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ADCS-ADL: 1.6 (95% CI: -0.2 to 3.3, p= 0.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild AD:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ADAS-cog11: -1.5 (95% CI: -3.0 to 0.0, p= 0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ADAS-cog14: -1.7 (95% CI: -3.5 to 0.1, p=0.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ADCS-ADL: 2.3 (95% CI: 0.2 to 4.4, p= 0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate AD:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ADAS-cog11: -0.9 (95% CI: -3.1 to 1.3, p= 0.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ADAS-cog14: -1.5 (95% CI: -4.1 to 1.1, p=0.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ADCS-ADL: 0.5 (95% CI: -2.6 to 3.5, p= 0.77)</td>
</tr>
<tr>
<td>Solanezumab – early vs. delayed-start</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXPEDITION -EXT&lt;sup&gt;1&lt;/sup&gt;</td>
<td>R, DB, NI</td>
<td>n=1322, mild AD</td>
<td>Mild AD:</td>
</tr>
<tr>
<td></td>
<td>184 weeks</td>
<td></td>
<td>- ADAS-cog14: 1.40 (lower limit of 90% CI: -0.75)</td>
</tr>
</tbody>
</table>

AD=Alzheimer’s disease; ADCS-ADL=Alzheimer’s Disease Cooperative Study-Activities of Daily Living scale; ADAS-cog11=11-item cognitive subscale of the Alzheimer’s Disease Assessment Scale; ADAS-cog14=14-item cognitive subscale of the Alzheimer’s disease Assessment scale; DB= double-blind; NI= non-inferiority; R=randomized

Summary

The results of the placebo-controlled trials, EXPEDITON 1 and EXPEDITION 2, were not significant for many of the outcome measures, including the primary outcomes, and failed to show cognitive improvement with solanezumab<sup>3</sup>. However, the results of EXPEDITION-EXT did show a continuation of benefits seen in the placebo-controlled portion of the study through the delayed-start portion of the study<sup>1</sup>. These results, as available, only support the initiation of this treatment as early as possible in patients with mild AD<sup>1,3</sup>. The study should be acknowledged for its novel delayed-start design in this field. The authors acknowledge the lack of statistically significant results in the data surrounding the MMSE and CDR-SB scales and agree caution is
warranted in conclusions drawn from the results of the EXPEDITION-EXT study. The results of the EXPEDITION 3 study may give better insight as to where solanezumab may fit into treatment for AD. Further studies may be warranted to determine if solanezumab may be beneficial for patients that have Aβ build-up with the cognitive symptoms associated with AD, thus delaying the course of disease progression.1,9

Table 2. Incidence of adverse events in EXPEDITION trials.1,3

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Trial and AD severity</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIA-E</td>
<td>EXPEDITION 1 and EXPEDITION 2 Mild-to-moderate AD</td>
<td>Solanezumab vs. placebo: 0.9% vs. 0.4%; p=0.27</td>
</tr>
<tr>
<td></td>
<td>EXPEDITION 1, 2 and EXT-Mild AD</td>
<td>Early vs. delayed-start: 1.8% vs. 1.2%; p=0.50</td>
</tr>
<tr>
<td>ARIA-H</td>
<td>EXPEDITION 1 and EXPEDITION 2 Mild-to-moderate AD</td>
<td>Solanezumab vs. placebo: 4.9% vs. 5.6%; p = 0.49</td>
</tr>
<tr>
<td></td>
<td>EXPEDITION 1, 2 and EXT-Mild AD</td>
<td>Early vs. delayed-start: 14.3% vs. 12.7%; p= 0.41</td>
</tr>
<tr>
<td>Cardiac arrhythmia-related events</td>
<td>EXPEDITION 1 and EXPEDITION 2 Mild-to-moderate AD</td>
<td>Solanezumab vs. placebo: 5.0% vs. 3.7%; p=0.20</td>
</tr>
<tr>
<td></td>
<td>EXPEDITION 1, 2 and EXT-Mild AD</td>
<td>Early vs. delayed-start: 14.3% vs. 11.8%; p=0.19</td>
</tr>
<tr>
<td>Cardiac ischemia-related events</td>
<td>EXPEDITION 1 and EXPEDITION 2 Mild-to-moderate AD</td>
<td>Solanezumab vs. placebo: 1.8% vs. 1.2%; p= 0.36</td>
</tr>
<tr>
<td></td>
<td>EXPEDITION 1, 2 and EXT-Mild AD</td>
<td>Early vs. delayed-start: 3.8% vs.  2.6%; p=0.21</td>
</tr>
<tr>
<td>Deaths</td>
<td>EXPEDITION 1 and EXPEDITION 2 Mild-to-moderate AD</td>
<td>Solanezumab vs. placebo: 24 vs. 19*; no p-value reported</td>
</tr>
<tr>
<td></td>
<td>EXPEDITION 1, 2 and EXT-Mild AD</td>
<td>Early vs. delayed-start:4.9% vs. 3.6%; p= 0.28</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>EXPEDITION 1, 2 and EXT-Mild AD</td>
<td>Early vs. delayed-start:17.3% vs. 16.0%; p= 0.55</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>EXPEDITION 1, 2 and EXT-Mild AD</td>
<td>Early vs. delayed-start: 35.4% vs. 36.0%; p=0.82</td>
</tr>
</tbody>
</table>

ARIA-E=amyloid-related imaging abnormality-edema/effusion; ARIA-H=amyloid-related imaging abnormality-hemosiderin deposition

*Percentage not reported.

References

Sodium/Glucose Cotransporter (SGLT)-2 Inhibitors May Cause Ketoacidosis
Esra Mustafa, PharmD

Sodium glucose co-transporter-2 (SGLT-2) inhibitors represent a novel class of anti-diabetic drugs that are approved by the Food and Drug Administration (FDA) for use in patients with type 2 diabetes.\(^1\) SGLT-2 is expressed in the proximal tubules of the kidney and is responsible for the glucose reuptake from the glomerular infiltrate. By inhibiting this transporter, these drugs increase urinary glucose excretion thereby improving glycemic control in patients with type 2 diabetes. Medications in the SGLT-2 inhibitor class include canagliflozin, dapagliflozin, and empagliflozin.

Diabetic ketoacidosis (DKA) is a type of acidosis that more commonly occurs in patients with type 1 diabetes because of the lack of endogenous insulin production.\(^2\) This lack of insulin prevents use of peripherally circulating glucose to generate adenosine triphosphate. This then leads to hyperglycemia, ketone production, and metabolic acidosis. Patients with DKA usually present with hyperglycemia (>350 mg/dL), serum bicarbonate levels less than 10 mEq/L, and elevated ketones in the blood and urine. DKA is a common cause of high anion gap metabolic acidosis.\(^3\) An anion gap is calculated to assist in determining the cause of the acidosis in patients and is defined as the difference in measured cations and measured anions in the blood. A gap is considered high if >12 mEq/L.

In May of 2015, the FDA reported that SGLT-2 inhibitors have been associated with ketoacidosis in diabetic patients.\(^4\) The FDA had identified 20 cases of DKA that had been reported to the FDA Adverse Event Reporting System from March 2013 to June 2014,\(^4\) all of which occurred shortly after the initiation of SGLT-2 inhibitors. Notably, the cases included patients with type 1 or type 2 diabetes; patients presented with blood glucose levels that were normal or slightly elevated (<200 mg/dL). Most of the patients presented with high anion gap metabolic acidosis with elevated serum and urine ketones. The median time for symptom onset was about 2 weeks for the cases presented. Factors which may have contributed to DKA were identified in some of the patients; these included infection, urosepsis, reduced insulin dose, and reduced fluid and caloric intake. Factors which may have contributed to the high anion gap metabolic acidosis were also identified in some patients; these included acute renal failure, hypovolemia, hypoxemia, and history of alcohol use. These DKA cases were atypical as some of the patients were identified as type 2 diabetics and patients presented with normal blood glucose levels. Euglycemic DKA has been previously observed in patients who are fasting, or during prolonged activity, and pregnancy.\(^5,6\)
Literature evaluation

Reports of euglycemic DKA with use of SGLT-2 inhibitors

A single-arm, open-label study was conducted to determine the safety and efficacy of 8 weeks of treatment with empagliflozin on glycemia in patients with type 1 diabetes.⁷ Forty-two patients with type 1 diabetes were included in the study. Patients received 2 weeks of placebo followed by an 8-week treatment period with empagliflozin 25 mg once daily, and a 2-week post-treatment follow up period. To prevent hypoglycemia, both basal and prandial insulin doses were reduced by 30% and investigators made additional insulin dose adjustments based on patients’ capillary glucose levels. Two patients were withdrawn from the study after developing DKA within 3 days of empagliflozin initiation. These 2 patients were not included in any of the follow-up outcome measures. Total insulin doses were reduced by 70% and 50% after initiating empagliflozin for these patients. One of the patients presented with nausea and vomiting, plasma glucose 17.0 mmol/L (306 mg/dL), and pH 7.01; the second presented with nausea, plasma glucose 11.8 mmol/L (212 mg/dL), and pH 7.26. The initial glucose concentrations reported for these 2 patients were lower than the concentrations typically observed in DKA.²

These 2 patients had clinical factors (severe gastroenteritis and insulin pump failure) which may have triggered the DKA; however, the authors did not exclude the possibility that empagliflozin may have contributed to the pathogenesis of DKA.⁷ The large decrease in insulin doses for these 2 patients may have also played a role; decreased insulin levels may have caused an increase in rates of lipolysis in adipose tissue and ketogenesis in the liver, which would increase ketone levels in the body. The increased urinary glucose disposal caused by empagliflozin may have modified the clinical presentation of DKA, as both patients presented with blood glucose levels that are much lower than those usually observed in DKA. Further studies need to be conducted to evaluate if SGLT-2 inhibitors may contribute to the development of DKA by making patients more prone to produce ketones.

SGLT-2 inhibitors are currently being used off-label in clinical practice to treat patients with type 1 diabetes. A case report was recently published that discussed a patient with type 1 diabetes who developed euglycemic DKA after off-label use of canagliflozin.⁸ The patient presented to the emergency room complaining of malaise, nausea, and vomiting. The patient had a blood glucose of 139 mg/dl, serum bicarbonate of 14 mEq/L and an anion gap of 15 mEq/L. A urinalysis revealed urine ketones greater than 80 mg/dL and a urinary glucose level greater than 1 g/dL. The increased urinary glucose level was likely attributable to canagliflozin’s mechanism of action. The patient received 5% dextrose, half normal saline and an insulin infusion; the acidemia was quickly resolved and the patient was discharged after 2 days. This case study reinforces the recommendation that canagliflozin should not be used in patients with type 1 diabetes.

Another case report was of a patient with type 2 diabetes who developed euglycemic ketoacidosis after receiving 6 doses of canagliflozin 300 mg daily.⁹ The patient presented to the emergency room with worsening nausea, vomiting, and abdominal pain. She had a blood glucose level of 68 mg/dL, an anion gap of 19 mEq/L, moderate serum ketones, a serum bicarbonate of 9 mg/dL and glucosuria (>500 mg/dL). The patient’s past medical history included type 2 diabetes that was complicated by gastroparesis, which may have contributed to the gastrointestinal symptoms. The patient was treated with bicarbonate, 5% dextrose, and an insulin infusion and was discharged after 7 days.
Tofogliflozin is a SGLT-2 inhibitor that is being studied in Japan. A combined phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group study was conducted to assess the efficacy and safety of tofogliflozin in patients with type 2 diabetes. Two hundred-twenty nine patients were randomized to receive oral tofogliflozin 10, 20, or 40 mg, or placebo, once daily before breakfast for 24 weeks. Hyperketonemia and ketonuria were observed more in the tofogliflozin group than the placebo group. Total serum ketones significantly increased from baseline with increasing tofogliflozin dose. After 24 weeks of 10, 20, or 40 mg of tofogliflozin the total serum ketone levels increased by 0.0456 mmol/L, 0.0595 mmol/L, and 0.14 mmol/L from baseline, respectively (p<0.01). Interestingly, this increase in ketone body levels did not result in DKA. The authors hypothesized that the increased ketone levels may be due to an increase in lipolysis and mobilization of lipids to compensate for the loss of glucose in urine. The authors also stated that elevated ketones were unlikely due to DKA caused by extreme insulin deficiency because the decreases in fasting insulin levels in the tofogliflozin groups were small. This study revealed that the SGLT-2 inhibitors are associated with increased ketone production; however, the mechanism by which this occurs is not known.

Ketoacidosis with SGLT-2 inhibitors: potential mechanism

Literature has revealed that SGLT-2 inhibitor use in patients with type 2 diabetes may cause an increase in plasma glucagon levels, possibly to compensate for increased urinary excretion of glucose. In a double-blind trial, 18 males with type 2 diabetes were randomized to receive either dapagliflozin 10 mg/day (n=12) or placebo (n=6) for 2 weeks. Approximately 1 hour after dapagliflozin was administered, plasma glucose concentration declined from 167 to 153 mg/dl. The plasma glucagon concentration increased significantly compared to baseline; the glucagon levels reached a peak of 79 ± 8 pg/ml in patients taking dapagliflozin about 240 minutes post-administration. On days 3 and 14 of treatment, plasma glucagon remained significantly elevated in the dapagliflozin group compared to baseline and in the placebo group. The fasting plasma glucagon concentration increased from 64 ± pg/ml on day 1 to 85 ± 7 pg/ml on day 3 (p<0.05). On day 14, the fasting plasma glucagon concentration remained significantly increased at 77 ± 6 pg/ml (p<0.05) when compared with baseline (64 ± 4 pg/ml).

An increase in plasma glucagon was observed in the patients that received dapagliflozin and not in the patients treated with placebo, despite both groups having similar decreases in plasma glucose. This may be explained by the fact that SGLT-2 is present on the alpha cells of the pancreas. It is hypothesized that SGLT-2 inhibitors stimulate the alpha cells and promote glucagon secretion. It has previously been shown that increased glucagon levels have promoted hepatic ketogenesis. Thus, by increasing glucagon levels, SGLT-2 inhibitors promote ketogenesis, which may result in DKA.

In an open-label study, 66 patients with type 2 diabetes received empagliflozin 25 mg/day and were evaluated at baseline, after a single dose, and after 28 days of therapy. After a single dose of empagliflozin, plasma glucagon levels were significantly increased compared to baseline. Plasma glucagon increased from 18 ± 8 pmol/L to 20 ± 7 pmol/L (p=0.0378). After 28 days of therapy glucagon levels were nonsignificantly increased compared to baseline (18 ± 8 pmol/L) at 19 ± 7 pmol/L.

When phlorizin, a nonselective inhibitor of SGLT-1 and SGLT-2 was given to dogs, investigators observed an increase in acetoacetate, a ketone body. If SGLT-2 inhibitors mimic the action of phlorizin, they too could increase the renal tubular reabsorption of acetoacetate. Studies evaluating the effect of selective SGLT-2 inhibitors on ketone body metabolism are needed to confirm this hypothesis.
Discussion

In summary, several cases of DKA have been reported with SGLT-2 inhibitor use in patients with diabetes, which have led the FDA to release a warning that SGLT-2 inhibitors may increase the risk of DKA. Although the mechanism by which this occurs has not been identified, literature suggests multiple possibilities. These include promotion of ketogenesis through an increase in glucagon, or reabsorption of ketone bodies. An increase in ketone production and/or reduced clearance of ketones may result in DKA.

Further investigation is necessary to determine whether SGLT-2 inhibitors contribute to the development of DKA through promotion of ketogenesis. Also, studies should be conducted to evaluate if certain patient characteristics or factors may lead to a higher risk of developing DKA with SGLT-2 inhibitor use. Studies examining the combination of SGLT-2 inhibitors plus an incretin mimic would be of great interest. Incretin mimetics (such as exenatide) inhibit glucagon and stimulate insulin secretion. Based on their mechanism of action, it can be hypothesized that the addition of an incretin mimic to an SGLT-2 inhibitor may reduce hepatic ketogenesis and may exert an additive effect in lowering blood glucose levels.

Considering the available evidence, providers should inform patients to report any signs or symptoms of DKA, including abdominal pain, nausea, and vomiting. In the cases presented, symptoms of DKA usually appeared within 2 weeks of initiation of SGLT-2 inhibitors. At this time, the FDA has not announced any changes to the drug labeling for SGLT-2 inhibitors with regard to these safety concerns. Further evidence is needed to confirm an increased risk for DKA with SGLT-2 inhibitor use.

References


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**Prescribing Beers Drugs in the Elderly: Concerns and Treatment Alternatives**

*Caitlin Hoar, PharmD*

The Beers Criteria for potentially inappropriate medication use in the elderly, developed and distributed by the American Geriatrics Society (AGS), has been incorporated by the Centers for Medicare and Medicaid Services as an integral part of their policies and practices. The Beers Criteria are now being used as a quality measure in the National Committee for Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS). Despite recent updates to the Beers Criteria, as well as availability of other tools to improve medication appropriateness in the elderly (namely, the Screening Tool to Alert doctors to Right Treatment [START] and Screening Tool of Older Persons’ potentially inappropriate Prescriptions [STOPP] criteria), inappropriate prescribing of medications in the elderly continues. Based on claims data from local, Western New York health maintenance organizations (HMOs), the top 3 classes of medications that continue to be prescribed despite their presence on the Beers list are non-benzodiazepine sedative hypnotics, tricyclic antidepressants (TCAs), and skeletal muscle relaxants (SMRs). This article will discuss the reasons for inclusion of each class on the Beers list and alternative options for each associated use.

**Non-benzodiazepine sedative hypnotics**

Non-benzodiazepine sedative hypnotics, also termed “Z-drugs” or “Z-hypnotics,” include zolpidem, eszopiclone, and zaleplon, and are indicated for treatment of insomnia. They are similar to benzodiazepines, the traditional treatment modality for insomnia, as Z-drugs also act on gamma aminobutyric acid (GABA) receptors and have similar central nervous system (CNS) side effects including drowsiness, fatigue, postural instability, and impaired cognitive and motor function. They have been marketed as safer alternatives to benzodiazepines due to their improved kinetic profile: Z-drugs have a short duration of action compared to benzodiazepines, they do not disturb sleep architecture, and are thought to have decreased residual effects. Subsequent studies have shown that Z-drugs are not as benign as originally thought, reporting an increased risk of adverse events such as memory impairment and confusion. Based on these concerns, the AGS strongly recommends avoiding chronic use (>90 days) of non-benzodiazepine hypnotics in the elderly.
The non-benzodiazepine hypnotics are associated with parasomniac behaviors including somnambulism (sleepwalking), sleep-eating, sleep-driving, sleep-sex, and nightmares.\(^2\) In addition, hypnotics, in general, may have adverse residual psychomotor effects including dizziness, postural instability and falls; falls in the elderly are associated with fractures and head injuries, which are associated with significant morbidity and increased healthcare costs, and death.\(^2,6-9\)

A recent prospective cohort study performed in Europe evaluated the associations between exposure to hypnotics and the risk of hip fracture among elderly patients.\(^4\) Results indicated an increased risk of hip fracture in patients using hypnotics. Overall, hip fractures were reported in 4.4% of the study population (39,938 of 906,422), and the standard incidence ratio (SIR) of hip fractures with use of hypnotics was 1.2 (95% confidence interval [CI] 1.1-1.2). Use of Z-hypnotics was associated with a higher excess risk of hip fracture at night (SIR 1.3, 95% CI 1.2-1.4). A sub-analysis of duration of exposure revealed an increased risk for hip fracture during the initial 14 days of treatment, indicating that short-term use, not only chronic use, may also be harmful.

A meta-analysis of randomized controlled trials evaluating sedative hypnotics in older patients examined and compared improvements in sleep quality and adverse events including cognitive impairment and psychomotor effects.\(^5\) A total of 24 studies, involving 2,417 patients, were included in the analysis; 830 were treated with a benzodiazepine, while 1,099 received a Z-hypnotic. Overall, the number needed to treat (NNT) for improvements in sleep quality was 13, while the number needed to harm (NNH) was 6. Though these numbers were calculated using differing studies, they suggest that adverse effects associated with use of sedative hypnotics may be more frequently observed than improvements in sleep quality. Importantly, comparisons of Z-hypnotics to benzodiazepines revealed no significant differences in sleep quality or adverse effects, including cognitive and psychomotor-type events.

Treatment alternatives for insomnia in the elderly include both non-pharmacologic and pharmacologic options. Non-pharmacologic treatment recommendations include optimizing sleep hygiene (e.g., development of standard sleep-wake schedule, elimination of stimuli prior to retiring, elimination of daytime napping) and cognitive behavioral therapy.\(^6,10\) Pharmacologic treatment options for insomnia include melatonin, the melatonin-receptor agonist, ramelteon,\(^11\) and a handful of antidepressants.\(^12\) Tricyclic antidepressants (TCAs) are effective for treatment of insomnia,\(^6\) however, use of tertiary TCAs should be avoided in the elderly;\(^1\) reasons for avoidance are discussed in subsequent paragraphs. Doxepin is a TCA with histamine H\(_1\)-receptor antagonist activity and is an effective sleep aid with relatively few side effects at low doses (≤6 mg).\(^13\)

Other antidepressant alternatives to Z-hypnotics include trazodone and mirtazapine. Low-doses of trazodone may be used off-label for treatment of insomnia in the elderly; efficacy is due to antagonism of serotonin (5-HT\(_2\A\)) receptors and caution should be used with other serotonergic drugs due to risk of serotonin syndrome.\(^6\) Although not approved for treatment of insomnia, mirtazapine may be an effective alternative in elderly patients with comorbid depression and/or those who may benefit from appetite stimulation.\(^14,15\)

**TCAs**

TCAs are on the Beers list for multiple reasons.\(^1\) TCAs inhibit reuptake of norepinephrine (NE) and serotonin, while also affecting acetylcholine and histamine. Due to acetylcholine inhibition, TCAs exhibit anticholinergic effects. Anticholinergic adverse effects include urinary retention, constipation, xerostomia, confusion, and glaucoma.\(^15\) Additional side effects of TCAs include sedation, vivid dreams, weight gain, and orthostasis.
Sedation, coupled with anticholinergic effects, increases risk of falls and fractures in the elderly.\textsuperscript{9,16,17} TCAs may also prolong the QT interval and therefore increase the risk of arrhythmias and sudden death in patients at high risk of cardiovascular events.\textsuperscript{1,17} Due to their relatively narrow therapeutic index, complications arise when used concomitantly with cytochrome P450 (CYP) 2D6, 1A2, 2C19, and 3A4 inhibitors; inhibition of these enzymes may result in increased TCA levels and, consequently, increased incidence of adverse effects.\textsuperscript{17}

Tertiary TCAs are generally more concerning than secondary TCAs in elderly patients.\textsuperscript{1} Tertiary TCAs include amitriptyline, clomipramine, imipramine, trimipramine, and doxepin (>6 mg/day). Secondary TCAs, including nortriptyline and desipramine, are more selective for NE, and therefore have less adverse effects; doxepin is more specific for NE at low doses (<6 mg/day). Thus, secondary TCAs and low-dose doxepin may be considered as alternatives to tertiary TCAs in geriatric patients.\textsuperscript{1,15}

When examining other alternatives to TCAs, one should consider the indication and the patient’s comorbidities. TCAs are indicated for the treatment of depression and may be used off-label to treat multiple pain conditions, due to their effects on NE.\textsuperscript{6,18} Selective serotonin reuptake inhibitors (SSRIs) are generally well-tolerated and their use for treatment of depression in the elderly may be more appropriate.\textsuperscript{17,19} SSRIs may be optimal alternatives to TCAs for treatment of depression in the absence of pain, as SSRIs are not effective pain modulators.\textsuperscript{6} Examples of SSRIs include citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, and sertraline. Due to citalopram’s risk of QT prolongation and paroxetine’s anticholinergic activity, use of the other SSRIs should be considered initially.\textsuperscript{15}

In patients who are being treated for depression and have concomitant pain, use of a serotonin-norepinephrine reuptake inhibitor (SNRI) may be appropriate. SNRIs are thought to modulate pain by increasing synaptic NE, leading to upregulation of descending noxious inhibitory pain pathways.\textsuperscript{6} Duloxetine is indicated for the treatment of depression as well as diabetic peripheral neuropathy and fibromyalgia and may be appropriate for patients with pain, depression, and insomnia.\textsuperscript{18}

In a recent meta-analysis, Thorlund et al compared the safety and efficacy of SSRIs and SNRIs in older adults with depression.\textsuperscript{20} The investigators identified 15 randomized controlled trials for inclusion, involving 5 SSRIs (citalopram, escitalopram, paroxetine, fluoxetine, and sertraline) and 2 SNRIs (duloxetine and venlafaxine). Partial response rates were evaluated, as well as adverse effects. With regard to efficacy, higher response rates were observed with duloxetine (relative risk [RR] 1.62, 95% CI 1.26-2.05), paroxetine (RR 1.48, 95% CI 1.27-1.75) and sertraline (RR 1.28, 95% CI 1.07-1.51), compared to placebo. Of these, sertraline was associated with the lowest risk for dizziness (RR 1.14, 95% CI 0.65-1.83).

Other antidepressant alternatives to TCAs for use in the elderly include mirtazapine and bupropion.\textsuperscript{19,21} Mirtazapine is most appropriate if the patient displays signs of anxiety, insomnia, or anorexia. Mirtazapine exerts an anxiolytic effect, is effective in sedation, and stimulates appetite.\textsuperscript{14} If patients complain of somnolence with SSRIs or duloxetine, bupropion may be considered. However, bupropion lowers the seizure threshold and decreases appetite; therefore, its use is not recommended in patients with a history of seizures or anorexia.\textsuperscript{22}

**SMRs**

SMRs, including carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine are agents that should be avoided in the elderly.\textsuperscript{1} SMRs exhibit anticholinergic effects including dry mouth,
constipation, urinary retention, sedation, orthostatic hypotension, confusion, cognitive impairment, and delirium. In addition to the anticholinergic effects, SMRs are sedating; this combination of activity increases risk of falls and fractures in elderly patients and is associated with increased morbidity and healthcare costs.\(^9,23,24\)

Carisoprodol is associated with the highest risk of injury and is considered the least safe SMR.\(^24\) Carisoprodol is metabolized into an active metabolite, meprobamate, which is associated with sedation and CNS depression, abuse and dependence, and withdrawal effects similar to those of benzodiazepines.\(^6,24,25\) Cyclobenzaprine is a tricyclic drug, and the AGS likens it to amitriptyline.\(^26\) Cyclobenzaprine is highly anticholinergic and also carries a high risk of falls and fractures.\(^24,26\)

Pain experienced by the elderly is often associated with musculoskeletal disorders such as arthritis or degenerative spine conditions.\(^26\) Correct pain diagnosis is pivotal for effective treatment of pain. SMRs may relieve skeletal muscle pain caused by local tissue trauma or muscle strains; however, their effects are nonspecific and do not involve direct muscle relaxation. In patients experiencing pain due to spasticity, including conditions such as multiple sclerosis, or status-post stroke, treatment with spasmolytic agents would be warranted.\(^6,26\)

Spasmolytic agents to be considered include baclofen and tizanidine. Baclofen is a GABA type B agonist, whereas tizanidine is an alpha-2 adrenergic agonist; both are active at the dorsal root ganglion.\(^6,26\) These agents should be initiated at low doses and slowly titrated to achieve desired effect.\(^26\) Clinical studies have shown that baclofen and tizanidine have similar efficacy profiles;\(^27\) however, tizanidine has been associated with significant orthostatic hypotension.\(^6\) Thus, baclofen may be preferred in elderly patients.

**Conclusion**

With the incorporation of Beers Criteria into the NCQA HEDIS, there is additional incentive to practitioners to decrease prescribing of medications that should be avoided in the elderly.\(^1\) Per claims data from HMOs in Western New York, Z-hypnotics, TCAs, and SMRs are commonly prescribed. Notably, there are safe and effective alternatives to these drugs, and most are available in generic formulations. These options represent potential cost-savings to the patient and healthcare system, as well as cost-avoidance, with decreased risk of falls and fractures compared to their Beers counterparts.

**References**

Pre-Exposure Prophylaxis (PrEP) Guidelines

Drew W Cates, PharmD

What is PrEP?

Antiretroviral agents (ARVs) have been used in the treatment of human immunodeficiency virus (HIV)-positive individuals for over 20 years, but only recently have they been utilized as pharmacological prevention considered for individuals who are HIV-negative.1 Pharmacological prophylaxis involves the administration of prescription medications to those with specific risk factors or at high risk for development of an illness not yet present. Such interventions have proven useful in healthcare for many years. Examples of pharmacological prophylaxis include the use of angiotensin-converting enzyme-inhibitors prescribed to patients with diabetes at risk of renal complications, contraceptives to prevent pregnancy, and Malarone® (atovaquone/proguanil) or other antibiotics to prevent malaria. Pre-exposure prophylaxis (PrEP) is the utilization of ARVs to prevent HIV in uninfected individuals who are at risk of becoming infected with HIV.2 In July 2012, the Food and Drug Administration (FDA) approved the use of the first once-daily medication for PrEP.

On July 13, 2010, the White House released the National HIV/AIDS Strategy for the United States (US) stating:

“The United States will become a place where new HIV infections are rare and when they do occur, every person, regardless of age, gender, race/ethnicity, sexual orientation, gender identity or socioeconomic circumstances, will have unfettered access to high quality, life-extending care, free stigma and discrimination.”3

More recently, in May 2014, the Centers for Disease Control and Prevention (CDC) and United States Public Health Service (USPHS) jointly released the first comprehensive clinical practice guidelines for PrEP.1,2,4 Prior to the approval of PrEP and the release of the CDC/USPHS guidelines, HIV preventative measures were limited to education and physical barriers (i.e., condoms). At present, with the existence of PrEP, the goal is to further reduce the acquisition of HIV infection and its associated morbidity, mortality, and cost to individuals and society.2,4

Need for alternative HIV prevention methods

The CDC estimates that over 1.2 million people in the US are currently living with HIV, among which 168,000 are unaware they are infected.4,6 Many HIV-infected individuals do not receive treatment, with only 40% receiving regular medical care. Only 30% of individuals living with HIV maintain undetectable virus levels through combination antiretroviral therapy (cART), while an astonishing 70% have minimal-to-no virologic control. Several risk groups have been identified, including men who have sex with men (MSM), heterosexuals, and injection drug users (IDUs, see Figure 1). MSM represent 55% of patients living with HIV, while heterosexuals account for 25% and IDUs represent 14%.6 Overall, the incidence of HIV has been stable at approximately 50,000 new infections annually;4,6 however, the incidence has been increasing among MSM, particularly those aged 13 to 24 years (22% increase from 2008 to 2010).6,7

Many new infections are transmitted because people are unaware they are infected or are not virologically suppressed after diagnosis.5 Other survey data indicate that views surrounding HIV have changed, including a diminished sense of urgency, and a lack of interest in approaches to HIV prevention once deemed effective
These alarming data demonstrate the increased number of transmissions occurring in at-risk populations and the need for additional or alternative preventive measures.

New York State (NYS) has been identified in the top 5 states with the highest rates of HIV transmission. As a result of this staggering statistic, in June 2014, NYS Governor Andrew Cuomo announced a 3-point plan to decrease the annual number of new HIV infections, from approximately 3,000 to 750 by the end of 2020. These points included: identification of individuals with HIV and ensuring access to healthcare; initiating therapy in patients with HIV and maximizing viral suppression; and providing access to PrEP for non-infected individuals at high risk for HIV. In support of the Governor’s plan, NYS’ Ending the Epidemic Task Force produced the Blueprint document, outlining the 3 points as well as other recommendations to reduce the incidence of HIV and disease progression. These recommendations include implementation of a state-wide educational campaign on PrEP and non-occupational post-exposure prophylaxis (nPEP), as well as development of mechanisms to determine PrEP and nPEP usage and adherence, and cART adherence among individuals with HIV or acquired immune deficiency syndrome (AIDS).

As the number of people living with HIV continues to increase, the search for preventative measures becomes an integral step in the plan to abolish AIDS in the US, especially for those at high risk.

**Figure 1. Estimated new HIV infections in the US, 2010, for the most-affected sub-populations.**

![Graph showing estimated new HIV infections in the US, 2010, for the most-affected sub-populations.]

MSM=men who have sex with men; IDUs=Injection drug users

**CDC/USPHS-recommended therapy**

Tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) are 2 ARVs classified as nucleoside reverse transcriptase inhibitors (NRTIs). Through inhibition of viral reverse transcriptase, NRTIs prevent the assimilation of viral deoxyribonucleic acid (DNA) into human DNA. TDF is an analog of adenosine and FTC is an analog of cytosine, 2 of the basic building blocks of ribonucleic acid (RNA) and DNA, and because...
they lack 3’ hydroxyl groups, incorporation of these medications into an elongating strand of viral DNA causes premature DNA termination.

Recommended medications for PrEP include TDF and FTC, available in a combination product (Truvada®: TDF 300 mg/FTC 200 mg). Daily administration of TDF/FTC is recommended for HIV prevention in sexually active MSM and heterosexual men and women at substantial risk of HIV infection.

Clinical evidence

Several clinical trials have been conducted evaluating the efficacy and safety of PrEP in populations at high risk for HIV acquisition, including sexually active MSM and heterosexual men and women, and IDUs. These trials are summarized below and in Table 1 and Table 2.

MSM trials

PrEP Initiative (iPrEx) trial
The iPrEX study was a phase 3, randomized, double-blind, placebo-controlled, international trial involving men and male-to-female transgender individuals reporting sexual activity with a man in the 6 months prior to study initiation. There were 2,441 participants: 1,224 received TDF/FTC and 1,217 received placebo. Over the course of 2.8 years, investigators found a decreased risk of 44% in HIV infections with the TDF/FTC group. A comparison analysis of plasma and intracellular drug levels between the 36 newly acquired HIV participants and uninfected participants found inadequate drug concentration levels; thus, the investigators determined there was a 92% reduction in risk of HIV acquisition among those with detectable levels of TDF/FTC.

US MSM safety trial
The US MSM safety trial was a phase 2, randomized, double-blind, placebo-controlled study involving 400 MSM participants without HIV infection residing in 3 US cities: Atlanta, Boston, and San Francisco. The participants were randomly assigned in a 1:1:1:1 fashion to receive TDF (alone) or placebo, immediately or after a 9-month delay. The study period was 2 years; in this time, 7 participants acquired HIV. Three of these participants were in the initial placebo group, 3 were in the delayed TDF group (infection occurring prior to TDF administration), and 1 patient, assigned to the placebo group, was diagnosed with HIV at study enrollment.

Heterosexual men and women trials

Partners PrEP trial
Partners PrEP was a phase 3, randomized, double-blind, placebo-controlled study assessing the efficacy of once-daily TDF/FTC or TDF in acquiring HIV in 4,758 HIV-discordant heterosexual couples in Uganda and Kenya. The trial was stopped early after an interim analysis showed statistically significant differences favoring treatment over placebo. The estimated efficacy was 67% in the TDF group and 75% in the TDF/FTC group.

TDF2 trial
The TDF2 trial was a phase 2, randomized, double-blind, placebo-controlled study involving 1,219 heterosexual men and women in Botswana. In addition to efficacy, adherence was assessed. The efficacy of TDF/FTC in
## Table 1. Summary – HIV incidence findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome analyses – HIV incidence (mITT)</th>
<th>Effect: HR [efficacy estimate] (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Agent</td>
<td>Control</td>
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<tr>
<td>iPrEx (MSM)</td>
<td>36 infections among 1224 persons</td>
<td>64 infections among 1217 persons</td>
</tr>
<tr>
<td>US MSM safety trial</td>
<td>3 infections among 201 persons (all 3 in delayed arm, not on TDF)</td>
<td>4 infections among 199 persons (1 acute infection at enrollment)</td>
</tr>
<tr>
<td>Partners PrEP (heterosexual men and women)</td>
<td>TDF 17 infections among 1572 persons</td>
<td>52 infections among 1568 persons</td>
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<td></td>
<td>TDF/FTC 13 infections among 1568 persons</td>
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<tr>
<td>TDF2 (heterosexual men and women)</td>
<td>9 infections among 601 persons 1.2 infections/100 person-years</td>
<td>24 infections among 599 persons 3.1 infections per 100 person-years</td>
</tr>
<tr>
<td>FEM-PrEP (heterosexual women)</td>
<td>33 infections among 1024 person 4.7 infections per 100 person years</td>
<td>35 infections among 1032 persons 5.0 infections per 100 person-years</td>
</tr>
<tr>
<td>West African trial (heterosexual women)</td>
<td>2 infections among 427 persons 0.86 infections per 100 person-years</td>
<td>6 infections among 432 persons 2.48 infections per 100 person-years</td>
</tr>
<tr>
<td>VOICE (heterosexual women)</td>
<td>TDF 52 infections among 993 persons 6.3 infections per 100 person-years</td>
<td>35 infections among 999 persons 4.2 infections per 100 person-years</td>
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<tr>
<td></td>
<td>TDF/FTC 61 infections among 985 persons 4.7 infections per 100 person-years</td>
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<tr>
<td>BTS (injection drug users)</td>
<td>17 infections among 1204 persons 0.35 infections per 100 person-years</td>
<td>33 infections among 1207 persons 0.68 infections per 100 person-years</td>
</tr>
</tbody>
</table>

CI=confidence interval; FTC=emtricitabine; HIV=human immunodeficiency virus; HR=hazard ratio; mITT=modified intention-to-treat; TDF=tenofovir
Table 2. Measures of efficacy by medication adherence, percentage reduction in HIV incidence (95% confidence interval).

<table>
<thead>
<tr>
<th>Study</th>
<th>Modified intention-to-treat efficacy (95% CI)</th>
<th>Efficacy by adherence measures (95% CI)</th>
<th>Efficacy by blood detection of drug levels measures (95% CI)</th>
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<tr>
<td></td>
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<td>Self-reported</td>
<td>Pill-count</td>
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<td>iPrEx (TDF/FTC)</td>
<td>44% (15-63%)</td>
<td>&gt;50%: 50% (18-70%)</td>
<td>92% (40-99%)</td>
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<tr>
<td>Partners PrEP</td>
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<td>TDF2 (TDF/FTC)</td>
<td>All</td>
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<td></td>
<td>TDF: 67% TDF/FTC: 75%</td>
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<td>Men</td>
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<td>TDF: 63% TDF/FTC: 84%</td>
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<td>Women</td>
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<td></td>
<td>TDF: 71% TDF/FTC: 66%</td>
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<tr>
<td>TDF2 (TDF/FTC)</td>
<td>All</td>
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<td>Partners PrEP</td>
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<td>TDF: 71% TDF/FTC: 66%</td>
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<td></td>
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<tr>
<td>VOICE (TDF, TDF/FTC)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTS (TDF)</td>
<td>49%</td>
<td></td>
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</tbody>
</table>
| CI=confidence interval; FTC=emtricitabine; NR=not reported; TDF=tenofovir
| aNot statistically significant
comparison to placebo in both sexes was found to be 63% when medication adherence by pill counts was found to be 85% in both groups.

**FEM-PrEP trial**
The FEM-PrEP trial was a phase 3, randomized, double-blind, placebo-controlled study evaluating TDF/FTC efficacy in heterosexual women in South Africa, Kenya, and Tanzania. Therapy was discontinued in women who became pregnant during the study. This trial was stopped early, based on findings from an interim analysis suggesting that the study was underpowered. Notably, adherence was low among the trial participants, as determined by plasma samples. Fewer than 50% of women in the TDF/FTC group had detectable drug levels.

**Phase 2 trial among women in West Africa**
A randomized, double-blind, placebo-controlled trial was conducted in which oral TDF monotherapy was administered to heterosexual women in Ghana, Cameroon, and Nigeria. Two of the study sites closed prematurely due to operational issues; thus, data to assess efficacy were insufficient. Safety data showed the use of TDF resulted in no hepatic or renal adverse events among participants.

**Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial**
VOICE was a phase 2B, randomized, double-blind study comparing once-daily oral TDF, once-daily oral TDF/FTC, oral placebo, topical vaginal TDF, and topical vaginal placebo in 5,029 heterosexual women in eastern and southern Africa. The groups receiving once-daily oral TDF and topical vaginal TDF were stopped early after adherence and operational issues found these 2 groups to have unreliable efficacy results. The TDF/FTC group continued the trial as planned, but differences in efficacy results compared to placebo were not statistically significant. This was attributed to lack of adherence; <40% of participants had samples with detectable drug levels.

**IDUs trial**

**Bangkok TDF Study (BTS)**
BTS was a phase 3, randomized, double-blind, placebo-controlled study assessing once-daily oral TDF for HIV prevention among IDUs in Bangkok, Thailand. Participants were followed for a mean of 4.6 years. The efficacy of TDF was found to be 48.9% in the modified intention-to-treat analysis. The most common side effects reported were nausea and vomiting, which occurred more frequently with TDF compared to placebo but only in the first 2 months of administration. Differences between groups in the incidence of adverse events were not statistically significant; thus, TDF was deemed safe for HIV prevention in this population.

**Who qualifies for PrEP?**

In determining who qualifies for PrEP, clinicians should conduct a risk behavior assessment among patients at risk for HIV acquisition. Specific recommendations are outlined in Tables 3, 4, and 5.

Importantly, all patients should be screened for HIV prior to initiation of PrEP. Following initiation of PrEP, all patients should be monitored at least quarterly (every 3 months), to confirm HIV-negative status and assess side effects, adherence, and risk behaviors.
Table 3. MSM.$^2$

<table>
<thead>
<tr>
<th>All of the below</th>
<th>At least 1 of the following</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult man</td>
<td>Any anal sex (receptive or insertive) without condoms in the past 6 months</td>
</tr>
<tr>
<td>Without acute or established HIV infection</td>
<td>Any STI diagnosed or reported in the past 6 months</td>
</tr>
<tr>
<td>Any male sex partners in the past 6 months</td>
<td>Is in an ongoing sexual relationship with an HIV-positive male partner</td>
</tr>
<tr>
<td>Not in a monogamous partnership with a recently tested, HIV-negative man</td>
<td></td>
</tr>
</tbody>
</table>

HIV=human immunodeficiency virus; STI=sexually-transmitted infection

Table 4. Heterosexually active men and women.$^2$

<table>
<thead>
<tr>
<th>All of the below</th>
<th>At least 1 of the following</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult individual</td>
<td>Is a man who has sex with both women and men (behaviorally bisexual)</td>
</tr>
<tr>
<td>Without acute or established HIV infection</td>
<td>Infrequently uses condoms during sex with 1 or more partners of unknown HIV status who are known to be at substantial risk of HIV infection</td>
</tr>
<tr>
<td>Any sex with opposite sex partners in past 6 months</td>
<td>Is in an ongoing sexual relationship with an HIV-positive partner</td>
</tr>
<tr>
<td>Not in a monogamous partnership with a recently tested, HIV-negative man</td>
<td></td>
</tr>
</tbody>
</table>

HIV=human immunodeficiency virus

Table 5. IDUs.$^2$

<table>
<thead>
<tr>
<th>All of the below</th>
<th>At least 1 of the following</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult individual</td>
<td>Any sharing of injection or drug preparation equipment in the past 6 months</td>
</tr>
<tr>
<td>Without acute or established HIV infection</td>
<td>Been in a methadone, buprenorphine, or suboxone treatment program in the past 6 months</td>
</tr>
<tr>
<td>Any injection of drugs not prescribed by a clinician in past 6 months</td>
<td>Risk of sexual acquisition</td>
</tr>
</tbody>
</table>

HIV=human immunodeficiency virus

PrEPping pharmacists

PrEP has been shown to be effective in several trials, and pharmacists have the opportunity to significantly impact its success. Clinical pharmacists can educate patients on the administration and limitations of PrEP. Universally, clinical trials have shown that patients with drug adherence had more protection against HIV. Some PrEP clinical trials were ceased prior to study completion with low adherence as the major cause. Thus, it is important for pharmacists to educate about the importance of adherence and implement strategies for improvement. Strategies pharmacists can utilize include pill boxes, alarms, cell phones, diaries, and the support of family and friends. By working with patients directly, pharmacists can identify obstacles to adherence and help patients overcome these barriers.
Pharmacists can also inform patients of possible adverse effects that may occur while on PrEP. Nausea, vomiting, flatulence, headache, and dizziness are symptoms that many patients may experience when initiating therapy with TDF/FTC. Depending on severity, such side effects may discourage patients from taking the medication. Sometimes these side effects can be managed with non-pharmacological therapy.

Another role pharmacists could play in the administration of PrEP would be the screening for and management of potential drug-drug interactions. There are many interactions that can occur with Truvada® and other agents such as statins, diuretics, and aminoglycosides. Pharmacists are well-equipped to not only identify possible drug interactions but also to manage these interactions through direct patient interaction and interprofessional collaboration with other healthcare providers directly involved in the care of individuals with or at risk for HIV/AIDS.

Conclusion

The use of daily oral ARVs for PrEP should be considered in populations at high risk for HIV infection. Increased collaboration between pharmacists and other healthcare providers is encouraged to provide optimal patient-centered care, as the efficacy of PrEP is dependent upon medication adherence and regular medical visits for monitoring, counseling, and testing. Combined with other available preventative methods, PrEP is an important strategy for achieving an AIDS-free generation in the US.

References


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**Author Biographies**

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Dr. Mulcahy completed her pre-pharmacy curriculum at the University of South Carolina and received her Doctor of Pharmacy degree from the University of New England in Portland, Maine. She completed her PGY-1 pharmacy practice residency at the Buffalo Psychiatric Center (BPC) and has continued on as the current PGY-2 psychiatric pharmacy practice resident at the BPC. Dr. Mulcahy is looking forward to expanding her knowledge in psychopharmacology, neurology, addiction, and substance abuse. After completion of her residency, she plans to pursue a clinical position at a psychiatric facility, continue teaching pharmacy students, and obtain board certification in psychiatric pharmacy practice.

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Dr. Censi received her Bachelor of Science degree in Pharmacy Studies and completed the Doctor of Pharmacy program at Northeastern University in Boston, Massachusetts. She is currently a PGY-1 pharmacy practice resident at the UB/Middleport Family Health Center. Her professional interests include independent community pharmacy, ambulatory care, and education. She plans to pursue a career in 1 or more of these areas after completion of her residency.

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Dr. Pinski received her Bachelor of Science in Pharmaceutical Sciences at UB and completed her Doctor of Pharmacy degree at D’Youville College School of Pharmacy. She is currently a PGY-1 pharmacy practice resident at the UB/Middleport Family Health Center. Dr. Pinski has several years of experience in community pharmacy and is excited to expand on her knowledge in clinical disease state management, medication therapy...
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**Editors**

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Dr. Dunn received both her BS in Pharmacy and PharmD from the UB SPPS. She also completed a hospital pharmacy residency at New England Medical Center in Boston. She has had extensive experience as a pharmacist in various settings, including practicing in a traditional role in hospitals as a Clinical Pharmacy Specialist. She has also served as a Science Specialist at a law firm, working with a team of lawyers defending pharmaceutical companies in product liability lawsuits. In addition, she has participated on an FDA contract updating and rewriting drug labels. She is currently a Clinical Assistant Professor at the UB SPPS and Coordinator for the Center for Health Outcomes, Pharmacoinformatics, and Epidemiology (HOPE).

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Dr. Reilly received her PharmD from the University of Illinois at Chicago (UIC) College of Pharmacy after receiving her BA in Economics from the University of Chicago. She completed PGY-1 and PGY-2 residencies at the UIC College of Pharmacy, specializing in drug information. She is currently a Clinical Assistant Professor at the UB SPPS and Director of the New York State Medicaid Drug Information Response Center.

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