Exacerbations are frequently not reported by patients. After one exacerbation, a patient's lung function may never recover. Exacerbations may increase the risk of death.

References:

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CHAIRMAN’S LETTER

What makes a state physician friendly?

ike most things in life, choosing where to practice medi-
cine comes with pros, cons and trade-offs. Some physi-
cians want to practice in a big city, others a one-stoplight
town — and everything in between.

Often, where any of us end up pursuing our craft, physi-
cians included, doesn’t feel like a choice at all; life takes us
places, and family, lifestyle interests and a host of factors lead
us to where we end up. Any place where a person decides to
call home comes with pros and cons.

So our editors wanted to see if there were places in the
country that are more physician friendly. Are there objective
measures that make one place, perhaps, better for physicians
than another?

In the 2020 Best States to Practice project, Medical Econom-
ics® and our partner publication Physicians Practice® analyzed
publicly available data to provide a perspective on what states
can be best described as “physician friendly.”

For our analysis, our editors ranked the states based on
2019 data covering four categories: pay, cost of living, tax
climate, and physician density.

The list contained in this issue should not be taken as
ranking which states are better than others. A state with high
physician density, for example, may make competition fiercer,
but it may be like that because of an amazing climate and
great lifestyle amenities. Our list simply provides physicians
with some objective data they can use when making their
career decisions.

As always, please let us know how we’re doing by emailing
our editors at medec@mjhlifesciences.com. Our goal is to
provide you, our physician audience, with the practical con-
tent you need to help manage the myriad challenges facing
physicians today. We need your ideas, your questions and
your thoughts to make this publication the best it can be! 

Mike Hennessy Sr.
Chairman and Founder
of MJH Life Sciences
Careers
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Practical advice for physicians to consider as they make career choices.

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We rank every state on how physician friendly it is, based on physician pay, cost of living, tax burden and more.

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25 **Managing diabetes during COVID-19**
How physicians can use technology to help patients with diabetes remain adherent.

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How the pandemic is affecting malpractice and other liability concerns for physicians.

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Will changes improve the revenue potential of TCM programs?

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DAYVIGO® is an orexin receptor antagonist indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

DAYVIGO had no suggested physical dependence or association with rebound insomnia upon discontinuation

- There was no evidence of withdrawal effects upon drug discontinuation through 1 year of use, suggesting no physical dependence
- DAYVIGO contains lemborexant, a Schedule IV-controlled substance
  - Individuals with a history of abuse or addiction to alcohol or other drugs may be at an increased risk for abuse and addiction to DAYVIGO—follow such patients carefully

Get your patients started with a 5 mg dose

See how at DAYVIGOhcp.com

SELECTED SAFETY INFORMATION

CONTRAINDICATIONS
- DAYVIGO is contraindicated in patients with narcolepsy.

WARNINGS AND PRECAUTIONS
- Central Nervous System (CNS) Depressant Effects and Daytime Impairment: DAYVIGO can impair daytime wakefulness. CNS depressant effects may persist in some patients up to several days after discontinuing DAYVIGO. Prescribers should advise patients about the potential for next-day somnolence.
  - Driving ability was impaired in some subjects taking DAYVIGO 10 mg. Risk of daytime impairment is increased if DAYVIGO is taken with less than a full night of sleep remaining or at a higher than recommended dose. If taken in these circumstances, patients should not drive or engage in activities requiring mental alertness.
- Use with other classes of CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression, which can cause daytime impairment. Dosage adjustments of DAYVIGO and concomitant CNS depressants may be necessary when administered together. Use of DAYVIGO with other insomnia drugs is not recommended. Patients should be advised not to consume alcohol in combination with DAYVIGO.
  - Because DAYVIGO can cause drowsiness, patients, particularly the elderly, are at a higher risk of falls.

Please see additional Selected Safety Information on the following page and adjacent Brief Summary of DAYVIGO full Prescribing Information.

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SELECTED SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT’D)

• Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-Like Symptoms:
  Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions can occur with DAYVIGO. Prescribers should explain these events to patients. Symptoms similar to mild cataplexy can occur with DAYVIGO and can include periods of leg weakness lasting from seconds to a few minutes, can occur either at night or during the day, and may not be associated with identified triggering event (e.g., laughter or surprise).

• Complex Sleep Behaviors:
  Complex sleep behaviors, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake (e.g., preparing and eating food, making phone calls, having sex), have been reported to occur with the use of hypnotics such as DAYVIGO. Events can occur in hypnotic-naïve and hypnotic-experienced persons. Patients usually do not remember these events. Complex sleep behaviors may occur following the first or any subsequent use of DAYVIGO, with or without the concomitant use of alcohol and other CNS depressants. Discontinue DAYVIGO immediately if a patient experiences a complex sleep behavior.

• Patients with Compromised Respiratory Function:
  The effect of DAYVIGO on respiratory function should be considered for patients with compromised respiratory function. DAYVIGO has not been studied in patients with moderate to severe obstructive sleep apnea (OSA) or chronic obstructive pulmonary disease (COPD).

• Worsening of Depression/Suicidal Ideation:
  Incidence of suicidal ideation or suicidal behavior, as assessed by questionnaire, was higher in patients receiving DAYVIGO than placebo (0.3% for DAYVIGO 10 mg, 0.4% for DAYVIGO 5 mg, and 0.2% for placebo). In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions (including completed suicides) have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed at any one time. The emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

• Need to Evaluate for Comorbid Diagnoses:
  Treatment of insomnia should be initiated only after careful evaluation of the patient. Re-evaluate for comorbid conditions if insomnia persists or worsens after 7 to 10 days of treatment. Worsening of insomnia or the emergence of new cognitive or behavioral abnormalities may be the result of an unrecognized underlying psychiatric or medical disorder and can emerge during the course of treatment with sleep-promoting drugs such as DAYVIGO.

ADVERSE REACTIONS

• The most common adverse reaction (reported in 5% of patients treated with DAYVIGO and at least twice the rate of placebo) with DAYVIGO was somnolence (10% for DAYVIGO 10 mg, 7% for DAYVIGO 5 mg, 1% for placebo).

DRUG INTERACTIONS

• CYP3A Inhibitors: The maximum recommended dose of DAYVIGO is 5 mg no more than once per night when co-administered with weak CYP3A inhibitors. Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors.

• CYP3A Inducers: Avoid concomitant use of DAYVIGO with moderate or strong CYP3A inducers.

USE IN SPECIFIC POPULATIONS

• Pregnancy and Lactation: There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to DAYVIGO during pregnancy. Healthcare providers are encouraged to register patients in the DAYVIGO pregnancy registry by calling 1-888-274-2378. There are no available data on DAYVIGO use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

  There are no data on the presence of lemborexant in human milk, the effects on the breastfed infant, or the effects on milk production. Infants exposed to DAYVIGO through breastmilk should be monitored for excess sedation.

  • Geriatric Use: Exercise caution when using doses higher than 5 mg in patients ≥65 years old.

  • Renal Impairment: Patients with severe renal impairment may experience an increased risk of somnolence.

  • Hepatic Impairment: The maximum recommended dose of DAYVIGO is 5 mg in patients with moderate hepatic impairment. DAYVIGO is not recommended in patients with severe hepatic impairment. Patients with mild hepatic impairment may experience an increased risk of somnolence.

DRUG ABUSE AND DEPENDENCE

• DAYVIGO is a Schedule IV-controlled substance.

  • Because individuals with a history of abuse or addiction to alcohol or other drugs may be at increased risk of abuse and addiction to DAYVIGO, follow such patients carefully.

Please see adjacent Brief Summary of DAYVIGO full Prescribing Information.

Reference: 1. DAYVIGO (lemborexant) [Prescribing Information]. Woodcliff Lake, NJ: Eisai Inc.

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DAYVIGO® (lemborexant) tablets, for oral use, CIV
Initial U.S. Approval: 2019
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION 04/2020.

INDICATIONS AND USAGE
DAYVIGO is indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

DOSE AND ADMINISTRATION
Dosing Information
The recommended dosage of DAYVIGO 5 mg taken no more than once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. The dose may be increased to the maximum recommended dose of 10 mg based on clinical response and tolerability. Time to sleep onset may be delayed if taken with or soon after a meal.

Doseage Recommendations for Concomitant Use with CYP3A4 Inhibitors or CYP3A4 Inducers
In studies with concomitant use of CYP3A4 inhibitors or CYP3A4 inducers, the maximum recommended dose of DAYVIGO was 5 mg no more than once per night when co-administered with weak CYP3A4 inhibitors, co-administration with strong or moderate CYP3A4 inducers: Avoid concomitant use of DAYVIGO with strong or moderate CYP3A4 inducers. DAYVIGO has been evaluated in patients with hepatic impairment.

Daytime Rebound Effects
The maximum recommended dose of DAYVIGO is 5 mg no more than once per night in patients with moderate hepatic impairment. DAYVIGO is not recommended in patients with severe hepatic impairment.

CONTRAINDICATIONS
DAYVIGO is contraindicated in patients with narcolepsy.

WARNINGS AND PRECAUTIONS
CNS Depressant Effects and Daytime Impairment
DAYVIGO is a central nervous system (CNS) depressant that can impair daytime wakefulness even when used as prescribed. CNS depressant effects may persist in some patients for up to several days after discontinuing DAYVIGO. Prescribers should advise patients about the potential for next-day somnolence. Driving ability was impaired in some subjects taking DAYVIGO 10 mg. The risk of daytime impairment is increased if DAYVIGO is taken with less than a full hour of sleep remaining or if a higher than recommended dose is taken. If DAYVIGO is taken in these circumstances, patients should be cautioned against driving and other activities requiring complete mental alertness. Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression, which can cause daytime somnolence. Dose adjustments of DAYVIGO and of concurrent CNS depressants may be necessary when administered together because of potentially additive effects. The use of DAYVIGO with other drugs to treat insomnia is not recommended. Patients should be advised not to consume alcohol in combination with DAYVIGO because of addictive effects. Because DAYVIGO can cause dose-dependent, next-day residual effects, patients should be advised to limit their activities and avoid driving or operating hazardous machinery as a higher risk of next-day residual effects is present.

Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms
Sleep paralysis, an inability to move or speak for several minutes during sleep-wake transitions, and hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions, can occur with the use of DAYVIGO. Prescribers should explain these events to patients when prescribing DAYVIGO. Symptoms similar to mild cataplexy can occur with DAYVIGO. Such symptoms can include periods of leg weakness lasting from seconds to a few minutes, can occur either at night or during the day, and may not be associated with an identified triggering event (e.g., laughter or surprise). Complex Sleep Behaviors (complex sleep behaviors, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake e.g., preparing and eating food, making phone calls, having sex), have been reported to occur with the use of hypnagogics such as DAYVIGO. These events can occur in hypnagogic/naïve as well as in hypnic/experienced persons, Patients usually do not remember these events. Complex sleep behaviors may occur following the first or any subsequent use of DAYVIGO, or with the concurrent use of alcohol and other CNS depressants. DAYVIGO should be discontinued immediately if a patient experiences a complex sleep behavior.

Patients with Compromised Respiratory Function
The effect of DAYVIGO on respiratory function should be considered if prescribed to patients with compromised respiratory function. DAYVIGO has not been studied in patients with moderate to severe obstructive sleep apnea (OSA) or in patients with chronic obstructive pulmonary disease (COPD). Worsening of Depression/Suicidal Ideation
In clinical studies of DAYVIGO in patients with insomnia, the incidence of suicidal ideation or any suicide behavior, as assessed by questionnaire, was higher in patients receiving DAYVIGO than in those receiving placebo (0.8% for DAYVIGO 10 mg, 0.2% for placebo). In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions (including attempted suicide) have been reported. Suicidal tendencies may be present in such populations and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed at any one time. The emergence of any new behavior, sign or symptom of concern requires careful and immediate evaluation. Need to Evaluate for Co-morbid Diagnoses
Because sleep disturbances may be the presenting manifestation of a medical and/or psychiatric disorder, treatment of insomnia should be initiated only after careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric or medical illness that should be evaluated. Presence of insomnia or the emergence of new cognitive or behavioral abnormalities may be the result of an unrecognized underlying psychiatric or medical disorder and can emerge during the course of treatment with sleep-promoting drugs such as DAYVIGO.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of DAYVIGO was evaluated in 149 adult patients with insomnia disorder. jeg 18 to 89 years from two controlled efficacy trials (Study 1 and Study 2). Study 1 was a 6-month placebo-controlled trial assessing DAYVIGO 5 or 10 mg once nightly, followed by a 6-month parallel-group extension period in which patients initially treated with DAYVIGO continued on the same dose, and patients who received placebo were re-randomized to receive DAYVIGO 5, 10 mg once nightly. In Study 1, 44% patients were treated with DAYVIGO for one year. Study 7 was a 28-day placebo- and active-controlled trial assessing DAYVIGO 5 or 10 mg once nightly. Adverse Reactions Resulting in Discontinuation of Treatment
The frequencies of discontinuation due to adverse reactions in Study 1 (the first 30 days) and Study 2 were 2.6% and 1.1% for patients treated with 5 mg and 10 mg DAYVIGO, respectively, compared to 1.5% for patients in the placebo group. The most common adverse reactions leading to discontinuation of DAYVIGO were somnolence (0.1% for 13 mg, 0.7% for 5 mg, and 0.4% for placebo) and nightmares (0.5% for 10 mg, 0.2% for 5 mg, and 0% for placebo). The frequencies of discontinuation due to adverse reactions in the 6-month placebo-controlled period of Study 1 were 8.3% and 4.1% for patients treated with DAYVIGO 10 mg and 5 mg, respectively, compared to 3.8% for patients in the placebo group. The most common reasons for discontinuation of DAYVIGO and occurring in more than one patient with a treatment arm were somnolence (2.9% for 10 mg, 2% for 5 mg, 0.4% for placebo), nightmares (1.3% for 10 mg, 0.5% for 5 mg, and 0% for placebo), and palpitations (0.5% for 10 mg, 0% for 5 mg, and 0% for placebo). Concomitant Adverse Reactions
The most common adverse reaction reported in 3% or more of patients treated with DAYVIGO and at least twice the rate of placebo in Study 1 was somnolence (16% for DAYVIGO 10 mg, 7% for DAYVIGO 5 mg, and 1% for placebo). Table 1 presents the adverse reactions based on the pooled data from the first 30 days of Study 1 (8-month controlled efficacy trial) and Study 2 (11-month controlled efficacy trial) where the incidence was 2% in DAYVIGO-treated patients and greater than in placebo-treated patients.

Table 1: Adverse Reactions Reported in 2% of DAYVIGO-Treated Patients and at a Greater Frequency Than Placebo-Treated Patients During the First 30 Days of Study 1 and Study 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo</th>
<th>DAYVIGO 5 mg</th>
<th>DAYVIGO 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soma. or fatigue*</td>
<td>1.3</td>
<td>6.0</td>
<td>9.6</td>
</tr>
<tr>
<td>Headache</td>
<td>3.6</td>
<td>5.9</td>
<td>4.3</td>
</tr>
<tr>
<td>Nightmares or abnormal dreams</td>
<td>2.9</td>
<td>2.9</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*Combines preferred terms somnolence, orthostatic, fatigue, sluggishness

Other Adverse Reactions Observed During Clinical Trials
Study 1 and 2: Other adverse reactions of <2% incidence but greater than placebo are shown below. The following list does not include adverse reactions 11 for which a drug cause was remote. [2] that were as general as to be uninformative, or those that were not considered to have clinically significant implications.

- Sleep paralysis was reported in 1.5% and 1.9% of patients receiving DAYVIGO 10 mg and 5 mg, respectively, compared to no reports for placebo. Hypnagogic hallucinations were reported in 2.1% and 2.7% of patients receiving DAYVIGO 10 mg and 5 mg, respectively, compared to no reports for placebo.

- Two events of complex sleep behavior were reported, both in patients receiving DAYVIGO 10 mg.

DRUG INTERACTIONS
Drugs Having Clinically Important Interactions with DAYVIGO

Table 2: Clinically Important Drug Interactions with DAYVIGO

<table>
<thead>
<tr>
<th>Drug interaction</th>
<th>Clinical effect</th>
<th>Intended effect</th>
<th>Precautionary measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong, Moderate, and Weak CYP3A4 Inhibitors</td>
<td>Concentration with a strong, moderate, or weak CYP3A4 inhibitor increases clearance of DAYVIGO, which may increase the risk of DAYVIGO adverse reactions.</td>
<td>Avoid concomitant use of DAYVIGO with strong or moderate CYP3A4 inhibitors. The maximum recommended dose of DAYVIGO with weak CYP3A4 inhibitors is 5 mg.</td>
<td>Strong: CYP3A4 inhibitors: voriconazole, clarithromycin, Moderate: CYP3A4 inhibitors: tizanidine, varenicline, Weak: CYP3A4 inhibitors: chlordiazepoxide, carbamazepine.</td>
</tr>
<tr>
<td>Strong and Moderate CYP3A4 Inducers</td>
<td>Concentration with a strong or moderate CYP3A4 inducer decreases lamotrigine exposure, which may reduce DAYVIGO efficacy.</td>
<td>Avoid concomitant use of DAYVIGO with strong or moderate CYP3A4 Inducers.</td>
<td>Strong: CYP3A4 inducers: rifampin, carbamazepine, St John’s wort. Moderate CYP3A4 Inducers: bosentan, efavirenz, oxcarbazepine, modafinil.</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Concentration of alcohol increases lamotrigine Cmin and AUC. Co-administration of DAYVIGO with alcohol produces a numerically greater negative impact on postural stability and memory than when compared with alcohol alone when assessed near the Cmax of DAYVIGO (1 hours post-dose).</td>
<td>Avoid alcohol consumption with DAYVIGO.</td>
<td></td>
</tr>
</tbody>
</table>
**Table 2: Clinically Important Drug Interactions with DAVIEGO (cont’d)**

<table>
<thead>
<tr>
<th>Effect of DAVIEGO on Other Drugs</th>
<th>CPY2B6 Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact</strong></td>
<td>Concentration of DAVIEGO decreases the AUC of drugs that are CPY2B6 substrates, which may reduce the efficacy for these concomitant medications.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Patients receiving DAVIEGO and CPY2B6 substrates concurrently should be monitored for adequate clinical response. If the trough levels of CPY2B6 substrates may be considered as needed.</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>Bepridil, metoprolol.</td>
</tr>
</tbody>
</table>

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to DAVIEGO during pregnancy. Healthcare providers are encouraged to register patients to the DAVIEGO pregnancy registry by calling 1-888-787-2799.

**Risk Summary**

There are no available data on DAVIEGO use in pregnant women to evaluate for drug-associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal reproduction studies, oral administration of lemborexant to pregnant rats and rabbits during the period of organogenesis caused toxicities only at high multiples of the human exposure at the maximum recommended human dose (MRHD) based on AUC. The no observed adverse effect levels (NOAEL) are approximately 100 and 25 times the MRHD based on AUC in rats and rabbits, respectively. Similarly, oral administration of lemborexant to pregnant and lactating rats caused toxicities only at high multiples of the human exposure at the MRHD based on AUC. The NOAEL is 92 times the MRHD based on AUC. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All teratogenic effects have a background risk of birth defects, loss, or other adverse outcomes. In the U.S., population data, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively. Data: Animal Data: Lemborexant was administered orally to pregnant rats during the period of organogenesis in 2 studies at doses of 100, 300, and 1000 mg/kg/day, which are approximately 7 to 139 times the MRHD based on AUC. Lemborexant caused maternal toxicity, manifested by decreased body weight and food consumption, decreased mean fetal body weight, an increased number of dead fetuses, and skeletal, visceral, and visceral malformations (implants, cleft palate, and exencephaly). Male fetuses were exposed to approximately 120 times the MRHD based on AUC. The NOAEL of 100 mg/kg/day is approximately 143 times the MRHD based on AUC. Lemborexant was administered orally to pregnant rabbits during the period of organogenesis at doses of 10, 30, and 100 mg/kg/day, which are approximately 7 to 139 times the MRHD based on AUC. Lemborexant caused maternal toxicity that consisted of decreased body weight and food consumption and a higher incidence of skeletal variations (presence of cervical ribs and supernumerary lumbar ribs) at approximately 139 times the MRHD based on AUC. The NOAEL of 30 mg/kg/day is approximately 23 times the MRHD based on AUC. Lemborexant was administered orally to pregnant rabbits during pregnancy and lactation at doses of 10, 100, and 300 mg/kg/day, which are approximately 10 to 266 times the MRHD based on AUC. Lemborexant caused maternal toxicity that consisted of decreased body weight and food consumption and toxicity to offspring consisting of decreased pup weight, decreased pup length, and decreased acoustic startle responses at 266 times the MRHD based on AUC. The NOAEL of 100 mg/kg/day is approximately 93 times the MRHD based on AUC. Lactation Risk Summary: there are no data on the presence of lemborexant in human milk, the effects on the breastfed infant, or the effects on milk production, lemborexant and its metabolites are present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Infants exposed to DAVIEGO through breastmilk should be monitored for excessive sedation. The development, and health benefits of breastfeeding should be considered along with the mother’s clinical need for DAVIEGO and any potential adverse effects on the breastfed infant from DAVIEGO or from the underlying maternal condition.

**Pediatric Use**

The safety and effectiveness of DAVIEGO have not been established in pediatric patients. Geriatric Use: 81% of the total number of patients exposed to DAVIEGO (N=1,421) in controlled Phase 3 clinical trials were 65 years and over, and 67 patients were 85 years and over. Overall, efficacy results for patients ≥65 years of age were similar compared to patients ≥65 years, In a pooled analysis of Study 1 (time ≤30 days), and Study 2, the incidence of somnolence in patients ≥65 years with DAVIEGO 10 mg was higher (4.6%) compared to 3.7% in patients <65 years. The incidence of somnolence with DAVIEGO 5 mg was similar in patients ≥65 years (4.9%) and <65 years (5.1%). The incidence of somnolence in patients treated with placebo was 2% or less regardless of age. Because DAVIEGO can increase somnolence and drowsiness, patients, particularly the elderly, are at a higher risk of falls. Exercise caution when doses higher than 8 mg in patients ≥65 years old. Renal Impairment: no dose adjustment is required in patients with mild, moderate, or severe renal impairment. DAVIEGO exposure (AUC) was increased in patients with severe renal impairment. Patients with severe renal impairment on DAVIEGO on next-morning driving performance, impairment may experience an increased risk of somnolence. Hepatic Impairment: DAVIEGO has not been studied in patients with severe hepatic impairment. Use in this population is not recommended, DAVIEGO exposure (AUC) and C, and terminal half-life were increased in patients with moderate hepatic impairment (Child-Pugh class B), and terminal half-life was increased in patients with moderate hepatic impairment (Child-Pugh class C). Use in patients with moderate hepatic impairment is recommended with appropriate patient monitoring.

**Patients with Congenital Respiration Dysfunction**

In a study of patients with mild AS (pulmonary hypertension index >25 events per hour of sleep), DAVIEGO did not increase the frequency of apneic events or cause oxygen desaturation. DAVIEGO has not been studied in patients with COPD or moderate to severe ASA. Clinically meaningful respiratory effects of DAVIEGO in COPD or moderate to severe ASA cannot be excluded.

**DRUG ABUSE AND DEPENDENCE**

**Substance-Controlled Substances**

DAVIEGO contains lemborexant, a Schedule IV controlled substance. Abuse is the intentional, non-therapeutic use of a drug, even once, for its conceivable physiological or psychological effects, in a human abuse potential study conducted in recreational sedative abusers (≤29), lemborexant 10 mg, 20 mg (two times the maximum recommended dose), and 30 mg (three times the maximum recommended dose) produced responses on positive subjective measures such as “Drug liking,” “Overall Drug liking,” “Take Drug Again,” and “Good Drug Effects” that were statistically similar to those produced by the sedatives zopiclone (30 mg) and zolpidem (60 mg), and statistically greater than the responses on these measures that were produced by placebo. Because individual with a history of abuse or drug use may discontinue or discontinue use at a reduced risk for abuse and addiction to DAVIEGO, follow such patients carefully. Dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Animal studies and clinical trials evaluating physical dependence demonstrated that lemborexant did not produce withdrawal signs or symptoms upon drug discontinuation, This suggests that lemborexant does not produce physical dependence.

**OVERDOSAGE**

There is limited clinical experience with DAVIEGO overdose. In clinical pharmacology studies, healthy patients who were administered multiple doses of up to 75 mg (2.5 times the maximum recommended dose) of DAVIEGO showed dose-dependent increases in the frequency of somnolence. There is no available specific antidote to an overdose of DAVIEGO. In the event of overdose, standard medical practice for the management of any overdose should be used. In managing overdose, provide supportive care, including close medical supervision and monitoring and consider the possibility of multiple drug involvement. Consult a Certified Poison Control Center for the most up to date information on the management of overdoses.[1-800-222-1222 or www.poisong.org]. The value of dialysis in the treatment of overdose has not been determined with lemborexant. As lemborexant is highly protein-bound, dialysis is not expected to contribute to elimination of lemborexant.

**CLINICAL STUDIES**

**Special Safety Studies**

**Midle of the Night Safety:** The effect of DAVIEGO on midle of the night safety was evaluated in a randomized, placebo- and active-controlled trial in healthy female subjects ≥55 years or male subjects ≥65 years. Postural stability, the ability to awaken in response to a sound stimulus, and attention and memory were assessed following a scheduled awakening 4 hours after the start of the 6-hour time in bed. Postural stability was measured by assessing body sway upon an anti-slip meter. Nighttime diary, latency and mean sleep latency were measured (measured by body sway area at 4 hours as compared to placebo). The ability to awaken in sound of the midle of the night was assessed using an audiometer that delivered 1000 Hz tones up to 16 dB. There were no meaningful differences between DAVIEGO 15 mg or 10 mg and placebo on ability to awaken to sound, A computerized performance assessment battery was administered to assess attention and memory after the midle of the night awakening (4 hours postdose) in subjects receiving DAVIEGO 5 mg or 10 mg. DAVIEGO was associated with dose-dependent worsening on measures of attention and memory compared to placebo. Patients should be cautioned about the potential for midle of the night postural instability, as well as attention and memory impairment. Effects on Next-day Postural Stability and Memory: The effects of DAVIEGO on next day postural stability and memory were evaluated in two randomized, placebo- and active-controlled trials in healthy subjects and insomnia patients ≥55 and older. There were no meaningful differences between DAVIEGO 15 mg or 10 mg and placebo on next-day postural stability or memory compared to placebo. Effects on Driving: a randomized, double-blind, placebo- and active-controlled, four-week crossover study evaluated the effects of nighttime driving performance, Impairment on next-morning driving performance in adult and elderly subjects (compared with placebo) driving ability was impaired in some subjects taking 10 mg DAVIEGO. Patients using the 10 mg dose should be cautioned about the potential for next-morning driving impairment because there is individual variation in sensitivity to DAVIEGO. **Rebound Insomnia:** Rebound insomnia was assessed by comparing sleep latency recorded on ALS and SWABIO sleep recordings for the screening period to the two-week following treatment discontinuation in both Studies 1 and 2. Analysis of group means and the proportion of patients with rebound insomnia suggest that DAVIEGO was not associated with rebound insomnia following treatment discontinuation. **Withdrawal Effects:** In 12-month and 1-month continuation studies, safety and efficacy trials (Studies 1 and 2), nausea withdrawal effects were assessed by the Tyber Benedetoni Insomnia Withdrawal Symptom Questionnaire following discontinuation from study drug in patients who received DAVIEGO 5 mg or 10 mg, There was no evidence of withdrawal effects following DAVIEGO discontinuation at either dose. **DAVIEGO®** is a registered trademark of Eisai R&D Management Co., Ltd. and is licensed to Eisai Inc. ©2018 Eisai Inc. All rights reserved. DAVIEGO107543 10/2020
Using apps to reach patients
Increase engagement by finding the right apps for the right patients.

Humanize virtual care
How to make sure patients are satisfied with remote care options.

The importance of ‘digital vaccines’
What they are and how they can help with the COVID-19 pandemic.

3 things you should know about reversal of direct oral anticoagulants

3 things you should know about hereditary transthyretin amyloidosis
FASENRA is indicated as an add-on maintenance treatment of patients 12 years and older with severe eosinophilic asthma. FASENRA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

What could reducing exacerbations mean for your severe asthma patients?

**TEST** for elevated blood eosinophils (≥150 cells/µL)*1,2 with a simple blood test (CBC with differential).3,4

**TARGET** eosinophils directly with FASENRA, a biologic that provides near complete depletion of eosinophils in 24 hours.5-7 The mechanism of action and the relationship between the pharmacological properties and clinical efficacy has not been established.

**TREAT** with FASENRA for the POWER TO HELP PREVENT EXACERBATIONS and reduce oral corticosteroid use5,8-10.

HELP YOUR PATIENTS TAKE CONTROL OF THEIR ASThma

SCAN HERE TO LEARN MORE & SEE IF FASENRA IS APPROPRIATE FOR YOUR PATIENT

www.FASENRAOPTIONS.com

*Although not defined by clinical guidelines, one characterization of eosinophilic asthma can be a blood eosinophil count of ≥150 cells/µL.12

The pharmacodynamic response (blood eosinophil depletion) following repeat subcutaneous (SC) dosing was evaluated in asthma patients in a 12-week phase 2 trial. Patients received 1 of 3 doses of benralizumab [25 mg (n=6), 100 mg (n=6) or 200 mg (n=6) SC] or placebo (n=6) every 4 weeks for a total of 3 doses. Twenty-four hours post dosing, all benralizumab dosage groups demonstrated complete or near complete depletion of median blood eosinophil levels, which was maintained throughout the dosing period.5-7

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

Known hypersensitivity to benralizumab or excipients.

**WARNINGS AND PRECAUTIONS**

**Hypersensitivity Reactions**

Hypersensitivity reactions (eg, anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (ie, days). Discontinue in the event of a hypersensitivity reaction. Please see additional Important Safety Information on next page and Brief Summary of full Prescribing Information on adjacent pages.
FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma and an eosinophilic phenotype.

- FASENRA is not indicated for treatment of other eosinophilic conditions.
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus.

Please see BRIEF SUMMARY of FULL PRESCRIBING INFORMATION on adjacent page.

STUDY DESIGNS

SIROCCO AND CALIMA (Trials 1 and 2)

SIROCCO (48-week) and CALIMA (56-week) were 2 randomized, double-blind, parallel-group, placebo-controlled, multicenter studies comparing FASENRA 30 mg SC Q4W for the first 3 doses, then Q8W thereafter; benralizumab 30 mg SC Q4W, and placebo SC. A total of 1204 (SIROCCO) and 1306 (CALIMA) patients aged 12-75 years old with severe asthma uncontrolled on high-dose ICS (SIROCCO) and medium- to high-dose ICS (CALIMA) plus LABA with or without additional controllers were included. Patients had a history of ≥2 exacerbations requiring systemic corticosteroids or temporary increase in usual dosing in the previous year. Patients were stratified by geography, age, and blood eosinophil counts (≥300 cells/µL and <300 cells/µL). The primary endpoint was annual exacerbation rate ratio vs placebo in patients with blood eosinophil counts of ≥300 cells/µL on high-dose ICS and LABA. Exacerbations were defined as a worsening of asthma that led to use of systemic corticosteroids for ≥3 days, temporary increase in a stable OCS background dose for ≥3 days, emergency/urgent care visit because of asthma that needed systemic corticosteroids, or inpatient hospital stay of ≥24 hours because of asthma. Key secondary endpoints were pre-bronchodilator FEV1, and total asthma symptom score at Week 48 (SIROCCO) and Week 56 (CALIMA) in the same population.

ZONDA (Trial 3)

A 28-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter OCS reduction study comparing the efficacy and safety of FASENRA (30 mg SC Q4W for the first 3 doses, then Q8W thereafter; benralizumab (30 mg SC Q4W, and placebo (SC Q4W. A total of 220 adult (18-75 years old) patients with severe asthma on high-dose ICS plus LABA and daily OCS (7.5 to 40 mg/day), blood eosinophil counts of ≥150 cells/µL, and a history of ≥1 exacerbation in the previous year were included. The primary endpoint was the median percent reduction from baseline in the final daily OCS dose while maintaining asthma control.

REFERENCES

7. Data on File, REF-28001, AZPLP.
FASENRA® (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype [see Clinical Studies (14) in the full Prescribing Information].

Limitations of use:
- FASENRA is not indicated for treatment of other eosinophilic conditions.
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus.

DOSEAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.

General Administration Instructions

FASENRA is intended for use under the guidance of a healthcare provider. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended [see Warnings and Precautions (5.1) in the full Prescribing Information].

Administer FASENRA into the thigh or abdomen. The upper arm can also be used if a healthcare provider or caregiver administers the injection. Prior to administration, warm FASENRA by leaving carton at room temperature for about 30 minutes. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few translucent or white to off-white particles. Do not use FASENRA if the liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter.

Prefilled Syringe

The prefilled syringe is for administration by a healthcare provider.

Autoinjector (FASENRA PEN™)

FASENRA PEN is intended for administration by patients/caregivers. Patients/caregivers may inject after proper training in subcutaneous injection technique, and after the healthcare provider determines it is appropriate.

Instructions for Administration of FASENRA Prefilled Syringe (Healthcare Providers)

Refer to Figure 1 to identify the prefilled syringe components for use in the administration steps.

Figure 1

1. Grasp the syringe body, not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. The syringe may contain small air bubbles; this is normal. Do not expect the air bubbles prior to administration.

2. Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (for example, dropped without needle cover in place), discard and use a new prefilled syringe.

3. Gently pinch the skin and insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

4. Inject all of the medication by pushing in the plunger all the way until the plunger head is completely between the needle guard activation clips. This is necessary to activate the needle guard.

5. After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. Do not re-cap the prefilled syringe.

6. Discard the used syringe into a sharps container.

Instructions for Administration of FASENRA PEN

Refer to the FASENRA PEN Instructions for Use for more detailed instructions on the preparation and administration of FASENRA PEN [See Instructions for Use in the full Prescribing Information]. A patient may self-inject or the patient caregiver may administer FASENRA PEN subcutaneously after the healthcare provider determines it is appropriate.

CONTRAINDICATIONS

FASENRA is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients [see Warnings and Precautions (5.1) in the full Prescribing Information].

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred following administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, FASENRA should be discontinued [see Contraindications (4) in the full Prescribing Information].

Acute Asthma Symptoms or Deteriorating Disease

FASENRA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use FASENRA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

Eosinophilia may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA will influence a patient’s response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving treatment with FASENRA and do not respond to anti-helminth treatment, discontinue treatment with FASENRA until infection resolves.

ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:
- Hypersensitivity Reactions [see Warnings and Precautions (5.1) in the full Prescribing Information]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Across Trials 1, 2, and 3, 1,808 patients received at least 1 dose of FASENRA [see Clinical Studies (14) in the full Prescribing Information]. The data described below reflect exposure to FASENRA in 1,663 patients, including 1,556 exposed for at least 24 weeks and 1,387 across Trials 1, 2, and 3 from 48 weeks duration [FASENRA every 4 weeks (n=841), FASENRA every 4 weeks for 3 doses, then every 8 weeks (n=822), and placebo (n=847)]. While a dosing regimen of FASENRA every 4 weeks was included in clinical trials, FASENRA administered every 4 weeks for 3 doses, then every 8 weeks thereafter is the recommended dose [see Dosage and Administration (2.1) in the full Prescribing Information]. The population studied was 12 to 75 years of age, of which 64% were female and 36% were male.

Table 1. Adverse Reactions with FASENRA with Greater than or Equal to 3% Incidence in Patients with Asthma (Trials 1 and 2)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>FASENRA (N=847)</th>
<th>Placebo (N=847)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pharyngitis*</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Hypersensitivity reactions†</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

*Pharyngitis was defined by the following terms: ‘Pharyngitis’, ‘Pharyngitis bacterial’, ‘Viral pharyngitis’, ‘Pharyngitis streptococcal’.
† Hypersensitivity Reactions were defined by the following terms: ‘Urticaria’, ‘Urticaria popular’, and ‘Rash’ [see Warnings and Precautions (5.1) in the full Prescribing Information].
FASENRA® (benralizumab) injection, for subcutaneous use

26-Week Trial
Adverse reactions from Trial 3 with 28 weeks of treatment with FASENRA (n=73) or placebo (n=72) in which the incidence was more common in FASENRA than placebo include: headache (8.2% compared to 5.3%, respectively) and pyrexia (2.7% compared to 1.3%, respectively) [see Clinical Studies (14) in the full Prescribing Information]. The frequencies for the remaining adverse reactions with FASENRA were similar to placebo.

Injection site reactions
In Trials 1 and 2, injection site reactions (e.g., pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to benralizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Overall, treatment-emergent anti-drug antibody response developed in 13% of patients treated with FASENRA at the recommended dosing regimen during the 48 to 56 week treatment period. At 12% of patients treated with FASENRA developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to benralizumab in specific assays.

Postmarketing Experience
In addition to adverse reactions reported from clinical trials, the following adverse reactions has been identified during post approval use of FASENRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to FASENRA or a combination of these factors.

Drugs Interactions
No formal drug interaction studies have been conducted.

Use in Specific Populations

Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FASENRA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or by visiting mothertobaby.org/Fasenra

Risk Summary
The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. In a prenatal and postnatal developmental toxicity study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of benralizumab throughout pregnancy at doses that produced exposures up to approximately 310 times the exposure at the maximum recommended human dose (MRHD) of 30 mg SC [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk:
In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of pre eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data
Animal Data
In a prenatal and postnatal developmental study, pregnant cynomolgus monkeys received benralizumab from beginning on GD20 to GD22 (dependent on pregnancy determination), on 250 mg/kg/day for 14 days thereafter throughout the gestation period and 1 month postpartum (maximum 14 doses) at doses that produced exposures up to approximately 310 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 30 mg/kg once every 2 weeks). Benralizumab did not elicit adverse effects on fetal or neonatal development (including organ weight) or function up to 6.5 months after birth. There was no evidence of treatment-related external, visceral, or skeletal malformations. Benralizumab was not teratogenic in cynomolgus monkeys. Benralizumab crossed the placenta in cynomolgus monkeys. Benralizumab concentrations were approximately equal in mothers and infants on day 1, and the levels of benralizumab in infants were equal to or lower than mothers at later time points. Eosinophil counts were suppressed in infant monkeys with gradual recovery by 6 months postpartum; however, recovery of eosinophil counts was not observed for one infant monkey during this period.

Lactation
Risk Summary
There is no information regarding the presence of benralizumab in human or animal milk, and the effects of benralizumab on the breast fed infant and on milk production are not known. However, benralizumab is a humanized monoclonal antibody (lgG1a-class), and immunoglobulin G (IgG) is present in human milk in small amounts. If benralizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to benralizumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for benralizumab and any potential adverse effects on the breast-fed child from benralizumab or from the underlying maternal condition.

Pediatric Use
There were 108 adolescents aged 12 to 17 with asthma enrolled in the Phase 3 exacerbation trials (Trial 1: n=53; Trial 2: n=55). Of these, 46 received placebo, 40 received FASENRA every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received FASENRA every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV1<90%) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller therapy. The pharmacokinetics of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same FASENRA treatment. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies [see Adverse Reactions (6.1) in the full Prescribing Information]. The safety and efficacy in patients younger than 12 years of age has not been established.

Geriatric Use
Of the total number of patients in clinical trials of benralizumab, 13% (n=328) were 65 and over, while 0.4% (n=9) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients; and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Overdosage
Doses up to 200 mg were administered subcutaneously in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with benralizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Patient Counseling Information
Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use for FASENRA PEN) before the patient starts using FASENRA and each time the prescription is renewed as there may be new information they need to know.

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique using the FASENRA PEN, including aspic technique, and the preparation and administration of FASENRA PEN prior to use. Advise patients to follow sharp disposal recommendations [see instructions for Use in the full Prescribing Information].

Hypersensitivity Reactions
Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENARA. These reactions generally occurred within hours of FASENRA administration, but in some instances had a delayed onset (i.e., days). Instruct patients to contact their healthcare provider if they experience symptoms of hypersensitivity reaction [see Warnings and Precautions (5.2) in the full Prescribing Information]. Not for Acute Symptoms or Deteriorating Disease
Inform patients that FASENRA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA [see Warnings and Precautions (5.2) in the full Prescribing Information].

Reduction of Corticosteroid Dose
Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy [see Warnings and Precautions (5.3) in the full Prescribing Information].

Pregnancy Exposure Registry
Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FASENRA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting mothertobaby.org/Fasenra [see Use in Specific Populations (8.1) in the full Prescribing Information].

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Rev. 10/19 US-30569 10/19
Deciding where to practice: 7 tips

by Mark Rowh Contributing Author

It is hard to overstate the importance of some decisions. In the life of a physician, the choice of where to practice certainly falls into that category.

“Location can impact your daily practice, as well as your career trajectory and quality of life outside of work,” says Wade A. Brosius, D.O., a primary care physician at Spring-Ford Family Practice in Royersford, Pennsylvania, and acute care for elders medical director for Tandigm Health. “Choosing the right type of practice—large or small, independent or system-owned, single- or multispecialty—can also go a long way toward overall job satisfaction.”

The best time for making this choice varies. Sometime during the residency seems to be the best option for most physicians, with earlier starts allowing more time for exploration. But waiting until the third year is also acceptable if the delay is not too long, according to Travis Singleton, executive vice president of marketing and sales at Merritt Hawkins. “Given the dampening effect of COVID-19 on the job market, it’s better to job hunt earlier in the year and not wait until you are a few months out,” he says.

Regardless of timing, selecting where to practice merits careful investigation. In making your decision, consider these tips.

Don’t rule out the independent and/or small group route

Although large health care systems have much to offer, other possibilities may be worth considering. Independent or smaller groups may offer increased reward potential, more autonomy, less bureaucracy, greater flexibility and an ability to limit payors, says Reuben Elowitz, M.D., CEO of Private Health Dallas in Texas.

Of course, there can also be a downside, with the potential for increased financial risk, reduced negotiating power for contracts, reduced benefits, or fewer referrals. But for some physicians, smaller is simply a better match.

Explore multiple locations

It may be tempting to stick with the familiar, but that can be a mistake.

“In terms of geography, think outside the box,” Singleton says. “Don’t be bound by preconceptions.” Rather than limit your choices to a few areas you know, consider the qualities and options you want in a location, whether that means good schools, cultural and recreational amenities, or something as basic as safety.

Find peers with similar outlooks

Clive Fields, M.D., chief medical officer and cofounder of VillageMD in Houston, Texas, believes that identifying a work environment that’s a good cultural and clinical fit is essential. “Working with like-minded physicians is critical to long-term career satisfaction,” he says. If your clinical interest is in wellness and prevention, a practice with large skilled nursing or hospital obligations would likely not be a good fit. If you have a young family and specific family interests, look for organizations and locations that will give you both the time and opportunity to engage in those activities.

Continues on Page 14
While physicians are a source of strength in our communities, ISMIE is here to help sustain that strength.

Our Wellness Center – ismie.com/wellness – is continually evolving to better meet the needs of our policyholders, helping you navigate personal and professional challenges.

For answers to your COVID-19-specific questions, please visit ismie.com/COVID-19.
Like most things in life, choosing where to practice medicine comes with pros, cons and trade-offs. Some physicians want to practice in a big city, others a one-stoplight town — and everything in between.

But besides personal and lifestyle reasons, there are some states that are better for physicians than others in terms of finances, competition and other criteria.

In the 2020 Best States to Practice project, our partner publication Physicians Practice compiled some publicly available data to provide a perspective on what states can be best described as “physician friendly.”

For our analysis, our editors ranked the states based on 2019 data covering five categories:
- Average salary
- Highest/lowest malpractice premiums
- The 2019 cost of living index
- Tax climate (state collections per capita)
- Physician density
- Malpractice premium costs

Physicians Practice® obtained the data from publicly available sources.

Here’s a brief description of our methodology:
We ranked each state and the District of Columbia on the criteria described desirable outcome per criteria, then averaging those scores resulted in the ranks of the states below.

The list below should not be taken as ranking which states are better than others. It simply provides physicians with some objective data they can use when making their career decisions.

**Consider the family angle**

Unless you are totally on your own, any location decision should include family considerations.

“If the location is not the right fit for you and your family, that may not be the best practice for you,” says Gary Price, M.D., president of The Physicians Foundation. “I know of physicians who had the opportunity to practice their dream job in their dream city, but because their spouses were simply not happy there, they had to relocate.” In fact, that almost happened in Price’s case. He found a location and practice which seemed ideal, but his wife quickly realized that the area was almost devoid of young families. They looked elsewhere, finding an alternative that proved to be a better fit.

**Set a facilities timeline**

If the goal is starting a private practice rather than joining an existing one, facilities planning should commence up to two years in advance. When looking for space to lease, the search should begin 12 to 14 months ahead of the planned opening, according to Justin Brasell, executive vice president at Transwestern, a national commercial real estate firm. When looking to build a new property, physicians should start the site selection process 18 to 24 months before opening. This allows enough time for finding the site, negotiating the sale of the land, closing on the land, designing the facility, and constructing a new building.

**Seek the advice of insiders**

Andrew H. Rosenthal, M.D., medical director of plastic surgery at Modernizing Medicine in South Florida, advises supplementing research with personal insights. “Talk to those that came before as you are finishing residency,” he says. “Ask what the landscape and journey looked like for them.” Talking to people in a community where you might want to live can also be helpful, but keep in mind that their agendas can color the information offered. Insightful sources of information may include CEOs of hospitals in the area. “They are often more than willing to talk and will give you a good picture of the landscape,” Rosenthal says.

**Develop a checklist**

The American Medical Association (AMA) recommends creating a checklist for investigating and acting on practice choices. Such a list might include lifestyle factors, available practice options, steps in becoming practice-ready and key components of employment contracts.
Average salary

1 Utah & New Jersey: $264,470

2 Wisconsin: $249,110

3 Kansas: $246,670

4 Nevada: $237,320

5 South Carolina: $235,790

1 Utah $264,470
2 New Jersey $264,470
3 Wisconsin $246,700
4 Kansas $246,700
5 Nevada $237,320
6 South Carolina $235,790
7 Illinois $234,810
8 Arkansas $231,750
9 Idaho $228,620
10 Missouri $227,390
11 Mississippi $227,390
12 Alaska $226,600
13 Oklahoma $226,030
14 North Dakota $225,140
15 New Mexico $224,640
16 Wyoming $222,750
17 Vermont $221,700
18 Colorado $221,220
19 Oregon $220,960
20 Washington $220,960
21 South Dakota $218,620
22 Michigan $218,340
23 Nebraska $217,580
24 Texas $216,020
25 Kentucky $215,450
26 Tennessee $214,710
27 New Hampshire $214,710
28 Alabama $214,170
29 Florida $214,030
30 West Virginia $213,620
31 Iowa $213,340
32 Ohio $212,900
33 Georgia $211,670
34 Indiana $211,550
35 Louisiana $209,810
36 Arizona $209,810
37 Montana $208,470
38 Maine $207,110
39 Delaware $202,440
40 District of Columbia $202,440
41 Rhode Island $199,890
42 Pennsylvania $199,300
43 North Carolina $197,860
44 Minnesota $193,140
45 Connecticut $192,900
46 Virginia $191,110
47 New York $190,950
48 Maryland $186,760
49 California $176,120
50 Hawaii $175,250
51 Massachusetts $162,830
Tax collection per capita

1 Alaska: $1,608
2 New Hampshire: $1,859
3 Texas: $1,894
4 Florida: $1,917
5 South Carolina: $1,956

1 Alaska
2 New Hampshire
3 Texas
4 Florida
5 South Carolina
6 Arizona
7 South Dakota
8 Mexico
9 South Dakota
10 Alabama
11 Georgia
12 Oklahoma
13 Colorado
14 Louisiana
15 Montana
16 Ohio
17 Mississippi
18 Nebraska
19 Vermont
20 Idaho
21 North Carolina
22 Kentucky
23 Indiana
24 New Mexico
25 Washington
26 Kansas
27 Wyoming
28 Michigan
29 Oregon
30 North Dakota
31 Pennsylvania
32 Illinois
33 Maine
34 Rhode Island
35 Iowa
36 Wisconsin
37 Arkansas
38 West Virginia
39 Massachusetts
40 Utah
41 New Jersey
42 Delaware
43 California
44 Maryland
45 New York
46 Connecticut
47 Nevada
48 Minnesota
49 Hawaii
50 Virginia
51 District of Columbia

Worst
Best

1
2
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4
5

$1,608
$1,859
$1,894
$1,917
$1,956

$2,137
$2,150
$2,180
$2,354
$2,371
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$4,924
$5,015
N/A
Lowest malpractice rates

1 Mississippi: $3,469
2 Wisconsin: $3,623
3 Minnesota: $3,956
4 California: $4,168
5 Nebraska: $4,523
**CAREERS / BEST STATES TO PRACTICE 2020**

**Average cost of living index**

1. **Mississippi**: 84.80
2. **Oklahoma**: 86.50
3. **Arkansas**: 87.10
4. **New Mexico**: 88.20
5. **Missouri**: 88.50

- **Mississippi**: 3
- **Arkansas**: 87.10
- **Oklahoma**: 86.50
- **New Mexico**: 88.20
- **Missouri**: 88.50

**States with the lowest cost of living (Lowest numbers are best):**

1. Mississippi
2. Arkansas
3. Oklahoma
4. New Mexico
5. Missouri

**States with the highest cost of living (Highest numbers are best):**

35. Nevada
36. New Hampshire
37. Washington
38. Vermont
39. Maine
40. Rhode Island
41. Utah
42. New Jersey
43. Connecticut
44. Maryland
45. Alaska
46. Massachusetts
47. Oregon
48. New York
49. California
50. District of Columbia
51. Hawaii
Physician density

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1 Wyoming: 1,172
2 Alaska: 1,900
3 North Dakota: 2,015
4 South Dakota: 2,041
5 Montana: 2,326
Best States Ranked

1 Mississippi
2 Alaska
3 Idaho
4 Missouri
5 Kansas

18 Tennessee
19 New Hampshire
20 Alabama
21 Wisconsin
22 Vermont
23 Illinois
24 Florida
25 Utah
26 West Virginia
27 Iowa
28 Colorado
29 Ohio
30 Georgia
31 Indiana
32 Louisiana
33 Arizona
34 Oregon
35 Montana
36 Maine
37 Delaware
38 Washington
39 District of Columbia
40 New Jersey
41 Rhode Island
42 Pennsylvania
43 North Carolina
44 Minnesota
45 Connecticut
46 Virginia
47 New York
48 Maryland
49 California
50 Hawaii
51 Massachusetts
Implementing the Topcon ocular telehealth platform for diabetic retinopathy screening in primary care can increase number of screenings for diabetic retinopathy

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes, affecting more than two in five Americans with diabetes. The National Eye Institute expects the number of Americans with DR to reach more than 10 million by 2030 and 14.6 million by 2050. In the United States, DR causes approximately 80% of instances of legal blindness in people aged 20 to 74.

Patients typically experience DR as a slow, pain-free decrease in vision, with symptoms that can fluctuate and may include blurred, double or distorted vision; floaters; or refractive error changes. The spectrum of visual problems associated with DR — from minor vision problems to legal blindness — can substantially affect patients’ quality of life (QOL).

In addition to reduced QOL, DR is associated with high costs. In 2013, medical costs for retinal disorders in the United States were $8.7 billion, with nearly half — $4.1 billion — of these costs attributed to diabetes-related retinal disorders. Per-person-per-year medical costs for those with diabetic retinopathy are an estimated $3,640. Other nonmedical support resources — such as nursing home care, government purchase programs and guide dogs — and loss in productivity also can be costly. Results from a retrospective analysis on patients aged 40 or older with visual impairment showed that in 2004, all-cause visual impairment was associated with $10.96 billion in nursing home care costs and $13.7 billion in state and federal government spending.

**Importance of diabetic retinopathy screening**

Because DR typically shows no symptoms in beginning — and potentially through advanced — stages of disease, screenings are a critical tool for early detection and should be conducted annually for people with diabetes. With early detection and treatment, 95% of vision loss associated with DR can be prevented. In addition, adherence to guideline recommendations for DR screening and treatment may save the U.S. health system $600 million annually.

Despite the importance of annual screenings for DR, patient adherence is low. Approximately 50% of Americans with diabetes receive annual eye exams with dilation, and this rate is even lower in underserved and minority populations — an average of 10% to 12%. Patients who miss an annual eye exam report various contributing barriers, including transportation issues, illness, physical disability, too many other health care appointments, costs associated with the screening and not making the appointment with their eye care provider a priority.

To address these barriers to adherence, primary care providers (PCPs) and endocrinologists are beginning to incorporate telehealth-based DR screenings at point of care in their clinics. Traditionally, eye care practitioners have been the primary providers of DR screenings. However, at least 90% of patients with diabetes are treated by a PCP, which often puts PCPs in the position of initial point of contact with the patient. PCPs can leverage their access to patients with diabetes to help increase the rates of early DR detection and treatment by referring patients to eye care practitioners when needed.

**Value of telehealth-based screenings and barriers to implementation**

Telehealth-based DR screenings offered by PCPs and endocrinologists at point of care can increase patient access to screening, thereby helping to improve clinical outcomes. Providers can also benefit from offering annual DR screening at the point of care, as reimbursement rates are increasingly tied to meeting quality measures such as DR screening. For example, the Centers for Medicare & Medicaid Services (CMS) has a Merit-based Incentive Payment System (MIPS) that includes a measure for DR screening; the final provider performance...
scores given by MIPS influence reimbursement.\textsuperscript{14,15} Likewise, the Healthcare Effectiveness Data and Information Set (HEDIS) serves as a performance improvement tool, with scoring based on 90 performance measures, one of which includes DR screening on patients 18 to 75 years old with diabetes.\textsuperscript{16,17} HEDIS scores serve as highly credible indications of quality care. More than 90% of health plans use HEDIS to measure quality performance,\textsuperscript{18} and more than 190 million patients are enrolled in these plans.\textsuperscript{16}

**Topcon Screen Program**

The Topcon Screen program, a telehealth platform that uses robotic instruments and an interconnected reading network of board-certified clinicians for DR screening, is an example of a telehealth-based tool that has helped increase rates of DR screening among patients with diabetes when coupled with additional initiatives.\textsuperscript{19} It has helped providers meet HEDIS requirements for DR screenings.\textsuperscript{16,17}

Topcon Screen was developed to help effectively detect DR at point of care, increase screening rates among patients with diabetes and support practice referrals for all eye care practitioners. The program addresses common barriers to implementation through its straightforward, time-efficient process. A small-footprint robotic camera performs the screening in less than two minutes (automatically capturing both eyes within a single exam) and automatically transfers the images to Topcon’s reading network, where they are graded and signed by board-certified ophthalmologists within 24 hours and then returned with a completed analysis report.\textsuperscript{20,21} Subsequently, the patient’s chart or electronic medical record can be updated with the results and tagged as having met the HEDIS measure requirement.\textsuperscript{13} Topcon Screen manages the entire workflow and provides all necessary hardware, software, staff training, installation and reading network. The camera provided by Topcon Screen occupies only 1 foot of space and can be leased month to month, thereby eliminating any upfront cost or capital investment.\textsuperscript{19,20} Topcon Screen is reimbursed by most insurance companies, and it offers resources for questions or concerns regarding reimbursement.\textsuperscript{20,22}

**Topcon Screen Program interventions and results**

Positive results from telehealth-based screenings using Topcon cameras were recently experienced by Valley Medical Group (VMG), an ambulatory medical group practice in New Jersey that is part of a larger integrated health system. VMG participated in a 12-month Together 2 Goal Innovator Track Eye Care Cohort initiative to explore ways to standardize and increase DR screenings among the company’s 8,000 patients with diabetes treated across 30 primary care practices, two endocrinology practices and two ophthalmologists, all of whom share the same electronic health record (EHR). The group’s primary measure, which was adapted from a HEDIS measure, was the number of patients with diabetes in the cohort who had been documented for a DR screening. Key objectives included increasing the number of patients with diabetes in the cohort who had been documented for a DR screening. Key objectives included increasing the gap at the point of care for DR screening and documenting referrals to other providers and specialists.\textsuperscript{19}

Before the initiative, many of the group’s practices did not prioritize eye care for patients with diabetes, and staff did not understand the importance of DR screening. Communication gaps existed between primary care, endocrinology and ophthalmology. To address these concerns, the group implemented interventions such as educating staff and launching a DR screening clinic and telehealth-based screenings to give patients different options for eye care. In addition, a report was built using payer claims data that identified gaps regarding DR screenings, and staff streamlined eye care documentation in the EHR to ensure records were current. Patients who had not received a DR screening within the last year were flagged for education and eye examination scheduling. Staff communicated the importance of eye care to these patients using a tool that had been developed within the initiative to educate patients and increase engagement.\textsuperscript{19}

For the telehealth-based screenings, two Topcon TRC-NW400 retinal cameras were placed in the endocrinology practices. Retinal photos were read internally by the two ophthalmologists. Keeping the readings internal helped facilitate communication between the ophthalmologist, endocrinologist and patient and also offered staff the opportunity to hear feedback on how to improve the quality of the images. To minimize costs, the Topcon cameras were leased. Other efforts to reduce costs included using National Eye Institute educational resources, optimizing workflow and linking DR screenings to compensation to incentivize providers to increase screening rates.\textsuperscript{19}

During the four months the Topcon cameras were used, the medical group completed 120 images; 21% of the patients screened (n = 25) had DR and 30.5% of the patients (n = 36) had another eye disease. Identification of the eye disease resulted in “60 eyeballs saved,” according to VMG. As a result of all efforts combined over 12 months, the medical group experienced a 9.2% absolute increase in DR screening rates, from 40.7% to 49.9%. They also ranked in the 90th percentile for HEDIS quality measures for DR screenings and achieved a five-star rating.\textsuperscript{19}
Overcoming barriers to implementation

Although telehealth-based DR screening has become increasingly available, the United States has been slow to adopt the approach in comparison with other countries, such as the United Kingdom and Australia. A large barrier to implementation may involve incorporating diabetic retinopathy screening into existing workflows. A busy endocrinology practice, described in a retrospective longitudinal study, found that eye exams increased the time of an average 15- to 20-minute appointment by approximately eight minutes. Investigators compared compliance rates for diabetic retinal screening completed between December 31, 2016, and December 31, 2018, after implementing a point of service teleretinal DR screening program the first week of June 2017. Study results indicated that the time invested in conducting the screening and the follow-up appointment detracted from time for other tasks. Other concerns noted in the study included insurance reimbursement (low reimbursement, insurance nonpayments or lack of insurance) and the cost of purchasing a retinal camera.

To address workflow challenges associated with the entire initiative to increase DR screening, the VMG described above coordinated communication among billers, practice managers, office staff and ophthalmology to develop the optimal approach. The group prioritized ongoing communication and revisions that could improve workflow. In addition to developing a telehealth-based DR screening program, an onsite screening clinic was established for patients to attend in person if they preferred. For the telehealth program, the Topcon cameras were leased rather than purchased, and reimbursement for retinal photos ranged between $16 and $190. Most plans provide some type of reimbursement because they have incentives tied to quality ratings. PCPs can bill the global CPT codes 92250 or 92227, including an International Classification of Diseases, Tenth Revision (ICD-10) that supports diabetes to establish medical necessity.

Conclusions

The rate of DR across the United States is high and continues to grow, negatively affecting patient vision and quality of life and resulting in substantial costs to the health care system. DR screenings have served as an essential tool to help identify DR in its early stages, reduce rates of blindness and decrease costs. To tighten the care journey between primary care and eye care and enhance patient experience, telehealth-based screening options, such as Topcon Screen, have been increasingly offered at point of care. Continued efforts should be made to more widely implement DR screening options across the health care spectrum, helping to increase adherence rates and improve outcomes for patients.

Footnotes

a Medicare reimbursements may vary depending on region. Various federal and state incentives, quality assurance programs, and legislation may affect the coverage and reimbursement rates of both private insurance and Medicare and Medicaid plans. Topcon recommends that providers check with their patient’s insurance provider to verify reimbursement eligibility prior to screening.

b CMS issued a National Coverage Determination (NCD 80.6) authorizing Medicare coverage for fundus photography when used for the diagnosis of DR. In recent years, however, Medicare Administrative Contractors (MACs) in several jurisdictions have issued Local Coverage Determinations stating that those jurisdictions will not cover fundus photography for the diagnosis of diabetic retinopathy when performed by non-eye-care specialists. Thus, CMS coverage of fundus photography may vary by state and/or region and coverage should be verified with the relevant MAC.

c For asynchronous services such as Topcon Screen, there is no application of telehealth codes. The collection of data and the analyzing of those data take place at different times. For synchronous, real-time, bidirectional services between patient and provider, telehealth codes would apply. PCPs can bill the global CPT codes 92250 or 92227, including an International Classification of Diseases, Tenth Revision that supports diabetes, therefore establishing medical necessity.

Expert Interviews with Frank Manole, DNP, MBA, FAANP; and Laurie Shepard

Operations managers Manole and Shepard discuss how they were able to successfully implement the Topcon ocular telehealth solution into their practices and highlight the value of “closing care gaps” in diabetic retinopathy screening through comprehensive communication to establish goals and increase patient knowledge.
References
CHRONIC CONDITIONS

Frontiers in diabetes patient management

Innovative technology helps patients adhere to their treatment and stay safe during the COVID-19 pandemic

by Keith Loria Contributing author

Data has shown that diabetes increases a person’s susceptibility to severe COVID-19, making it especially important for those with diabetes to limit their potential exposure to the virus.

The COVID-19 health crisis has underscored the importance of having technology that helps medical professionals easily identify their patients with diabetes and verify their adherence with testing and office visits.

“When New York became a COVID-19 hot-spot, our providers understood that if patients failed to monitor and manage their blood glucose levels, miss routine follow-up touch points, or otherwise not receive the care they needed, they could be at increased risk of not just long-term complications, such as heart and kidney disease and vision and nerve problems, but short-term, potentially life-threatening issues such as severe low blood glucose levels or diabetic ketoacidosis,” says Jill Brodsky, M.D., FAAP, associate medical director, chair of the department of pediatrics, and pediatric endocrinologist at CareMount Medical in Poughkeepsie, New York.

Since the start of the pandemic, COVID-19 has presented both challenges and opportunities for diabetes management and technology.
Varun Goyal, CEO of Illuminate Health, notes that, on average, individuals with diabetes spend 66 minutes per day on self-care tasks, and since the pandemic, access to their medications and health care providers has become tricky.

“Thankfully, technology has become that enabler of care guidance for patients at home, while providing connectivity to their clinicians,” Goyal says. “Given that patients are holding off on health care services, there are risks of disease progression and even potential hospitalization if patients do not take care of themselves.”

Innovation Abounds
One of the most important technologies in recent years is the Continuous Glucose Monitoring (CGM) device, which eliminates the need for finger-prick glucose testing. CGMs continue to evolve, becoming less invasive, more accurate and easier for patients to use.

“CGM use provides real-time information to patients and their caregivers about blood sugar levels and provides alerts and alarms to the patient to immediately inform them when their blood sugar leaves the target range established by their provider,” Brodsky says. “Some CGMs enable patients to scan a reading device across the sensor to get readings, while others provide continuous readings via a Bluetooth connection between their CGM and their cellphone or smartwatch.”

Additionally, through integration with insulin pump therapy, CGMs can change the rate of insulin flow to minimize high blood glucose readings and reduce episodes of hypoglycemia.

All of these data can be shared directly with the patient’s provider at any time, virtually or in the office. This is particularly useful for patients who are uncomfortable venturing out during the pandemic.

Rise of Telehealth
Most health care experts agree that practices need an option for virtual visits for patients who don’t necessarily require an in-person visit but still need care from their provider.

Reza Mizani, M.D., FASN, founder and CEO of South Texas Renal Care Group in San Antonio, notes recent publications have shown that patients with Type 2 diabetes have 4 times the risk of death from COVID-19 and much longer hospital stays than those without the condition.

Therefore, it is crucial that patients with diabetes achieve HbA1C levels less than 6.5%. It also is important that patients prevent possible exposure to COVID-19 by avoiding high-traffic health care facilities such as hospitals and doctor’s offices.

“The use of telehealth during this era has been extremely beneficial in keeping our patients safe and continuing care,” Mizani says. “With [the Health Insurance Portability and Accountability Act] relaxing their rules and regulations, physicians have been able to reach their patients by utilizing Facetime and Google Duo, among other popular video communication platforms. I strongly believe in the use of this technology and recommend telemedicine stays in place with the appropriate insurance reimbursement.”

—Reza Mizani, M.D., founder and CEO, South Texas Renal Care Group, San Antonio

Visits can minimize patients’ risk of exposure while helping them maintain diabetic control through virtual engagement such as diet assessment, changes to medication or insulin titration.

Current Health’s remote monitoring platform integrates with Dexcom’s G6 continuous glucose monitor to provide physicians with the broadest picture of patient health possible.
“Remote monitoring provides real-time insight into patient health, allowing clinicians to spot patient deterioration early and intervene to avoid serious health issues,” he says. “For patients with diabetes, this could mean avoiding serious hospitalization events such as diabetic ketoacidosis or hypoglycemia by noticing early signs such a pulse and respiratory rate changes and derangement in glucose.”

Through clinical monitoring of these vital signs, providers can identify if a patient is not being adherent, or if their current therapy is not working, and act before a patient ends up in the hospital.

Kathleen Prendergast, M.D., chair of endocrinology and medical director of the University of Maryland Center for Diabetes and Endocrinology at the University of Maryland Baltimore Washington Medical Center, notes diabetes visits lend themselves well to the telehealth platform.

“Our practice transitioned to 100% telehealth during the shutdown in Maryland, and care for this population of patients was able to be continued with limited interruption,” she says. “Many patients hope that telehealth will remain an option even after the threat from the pandemic subsides. Telehealth does, however, work best if the patient has a smartphone so that a video call can be completed. Phone calls are utilized in cases when the patient does not have access to the video component and, while useful, often are not as fruitful as a video visit.”

Many patients with diabetes already were using technology on a day-to-day basis before the pandemic. Prendergast notes the use of insulin pumps and continuous glucose monitors, as well as “smart” glucometers or insulin pens, has risen significantly over the last several years.

“These devices can be uploaded to the cloud or emailed to the providers so that a great deal of data can be stored,” Prendergast says. “During the telehealth visit, this can easily be accessed and reviewed with the patient. These tech items have been demonstrated to improve diabetes control and increase patient satisfaction with their diabetes care.”

Teresa McArthur, senior vice president of clinical services for Cecelia Health, a virtual diabetes and chronic disease management startup, notes expanded digital and telehealth access has opened doors to reengage in care for individuals with diabetes who faced access barriers, such as the inability to take time off work for in-person appointments, transportation issues, or time associated with travel and appointment waits.

“With remote appointments, patients who may not have been within driving distance of an endocrinologist can now be prescribed continuous glucose monitoring, which has been proven to help patients manage their blood sugar levels,” she says. “Covid-19 made telehealth more than a critical channel; it proved telehealth’s value as the critical channel for ongoing chronic care management.”

**Communication Matters**

Because patients respond differently to different communication channels, physicians should consider a variety of technologies to connect with patients. In some cases, phone calls may be ideal. Other patients may respond best to secure texting, email or secure messaging via a patient portal, which supports secure communication between providers and patients and allows for prescription renewal requests and online scheduling.

“The portal is a useful tool that is convenient for patients and allows us to connect with patients who may have gaps in care,” Brodsky says. “We also use Salesforce as part of our patient engagement strategy, which gives us an efficient mechanism to communicate with patients sooner versus later.”

McArthur says smartphones provide tremendous opportunity to better link physicians with their patients, but a number of regulatory, access and adoption barriers have prevented the smartphone from becoming the gold standard in physician-patient communications.

“We’ve found in our populations that it’s still advisable that physicians adopt an omnichannel approach that incorporates video, audio and digital options when looking to foster dialogue with patients,” she says. “Given the hyper-individualized nature of managing diabetes, there is no one silver bullet technology or service that has shown complete effectiveness at addressing barriers to diabetes self-management. So it’s crucial that people in remote monitoring programs have access to the spectrum of management resources, rather than being limited by a payer or program to a single solution.”

That means the most effective remote management approach must incorporate a blend of human touch via expert clinical coaching and familiarity with various technologies so patients understand how their devices work and care teams can respond to any “red flags” identified either by the participant or by an abnormal lab value transmitted by their device.

“The future integration of doctor’s offices with the increased connectivity of CGM devices such as Dexcom, FreeStyle Libre, among others, will greatly enhance patient adherence moving forward,” Mizani says. “
Physician liability during COVID-19

by Todd Shryock Managing Editor

The COVID-19 pandemic has brought a lot of unknowns into the practice of medicine. Doctors are already dealing with diagnosing and treating people affected by the deadly virus while trying to keep themselves and their staffs safe from infection. But with the threat of infection also comes the threat of being sued for not taking the proper precautions against it. Medical Economics® spoke with Stephanie Sheps, vice president of claims for Coverys, a medical liability insurance provider, to discuss liability risk in the age of COVID. The following transcript has been edited for clarity and brevity.

Medical Economics®: What new liability threats have emerged from COVID-19?

Stephanie Sheps: First, there are the obvious risks that include transmission of COVID, both to patients and to staff. It’s a novel issue because we’re not fully understanding this virus yet, so things continue to evolve daily. Based on patient and provider awareness and precautionary measures taken to mitigate these risks, I believe that the greater liability actually stems from pandemic-related or contextual realms. And so, pandemic risks are those that do not involve the diagnosis or treatment of COVID-19, or the transmission of it, but are related to the changes in how healthcare is currently being delivered or not delivered. These risks include the denial of services to patients because of lack of capacity, or the availability of PPE, and provider and facilities that delay elective surgeries because of capacity issues, etc. Another significant area of risks stem from the fact that many providers have and continue to defer their primary care visits, their annual checkups of patients, routine screenings like mammograms and colonoscopies, things that we do to manage chronic conditions. And the fact that those are being deferred or if they’re being held, are being held virtually, does present some risk. I mean, there’s a reason we see our providers in person, they get to put eyes on the patient, they get to take labs, they get to really assess the patient using all of their senses. And so when that is being limited by doing these types of visits through telehealth, I think that could present some greater risk in the future. And just one final note is that on the patient side, many people are making the choice to delay or defer treatment, because they’re fearful of going into the doctor’s office or a hospital, or they’re trying to be a good citizen and think their issue isn’t that serious. [They say] other people need the facilities more, I will just hang back. And because they make those decisions, sometimes, we’ve seen increased risks of heart attacks and strokes that are having greater morbidity and mortality, because people are waiting it out at home. You’ve even seen some cases of delayed setting of fractures, because people just thought I’ll wait this out, it’s not that bad. And the longer they wait to deal with those issues, the more morbidity there could be.
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Sheps: Well, I think it’s a good starting place, and of course, would advise everybody to continue to follow those guidelines, but it’s not the panacea to prevent claims and suits. In essence, the standard of care is going to come from the region, the whatever the law is the common law, the statutory law in that jurisdiction, that will define the standard of care. Now we’re functioning under what we like to think of as a crisis standard of care right now, but only time will tell how things are perceived and adjudicated in the courts. So it’s always a good idea to follow the CDC guidelines. But unfortunately, I can’t say that it will be totally preventative of claims.

ME: Are there common mistakes or oversights that make practices more vulnerable to COVID-19-related lawsuits?

Sheps: I would say yes and no. And the reason I equivocate there is that these are common issues that would have existed before COVID. So the failure to document informed consent or informed refusal of treatment, those are risks that exist, no matter what. Obviously, there are these specific risks that patients will get the disease or transmit the disease to your staff while they’re there. But I think to me, the greatest risk right now is that providers are so focused on patient safety and risk mitigation efforts.

Sheps: We are not yet really there, as it is a little bit early in the lifecycle of what are potential suits or suits related to COVID-19. Not many have been filed yet that are very specific to COVID-19 and that aren’t just contextual or pandemic-related. But it takes some time for things to wind their way through the court system. There was one decision in the federal district court in New York, that actually remanded a case that was filed in the federal courts extensively, to bring certain allegations that were federal in nature, but it was remanded back to the states so that it wouldn’t have the protections of the PREP Act.

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ME: The states that have passed legislation that helps protect businesses from COVID-related lawsuits—do these laws help medical practices as well?

Sheps: Absolutely, they do. And the one that provides the broadest protection is the federal extension of the PREP Act, which happened back in March of this year. And what the PREP Act does is it provides immunity to certain individuals, in this case, medical or health care providers, for countermeasures taken to deal with health crises during this period of time. Many states have taken the initiative to invoke their own state-related liability protections and some of those are even stronger and broader and more encompassing, to protect health care providers, than the PREP Act itself. So there really are good protections out there for health care providers. But like anything else, there are ways around them.

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available, the dates of any declaration of a state of emergency in your jurisdiction.

We want to know the dates where maybe PPE was limited, or there were issues with ventilators, if we didn’t have enough ventilators, for patients in the inpatient setting. Any dates relating to staffing shortages, furloughs, or reallocations, a lot of staff in the hospital or long-term care setting are having to figure out new parts of their facility, new jobs within the facility to maintain the patient population and their employment. All of these dates are critical to being able to set the stage and not have to go back three to four years from now to figure out and put the pieces together of what has transpired.

In terms of record keeping, it’s very important that we have all of the documents that are related to some of those dates on the timeline. So that could be documents related to when we ordered PPE and that PPE was not available. Make sure that we’ve got pure documentation, including the purchase orders, or letters from suppliers saying, we don’t have masks available for the next six months, whatever those things may be, where your supplies were diverted, or anything that back up the situation that has been occurring while you’re trying to deliver patient care. It’s also important to have records of patient logs in terms of when they had visitors and when they left, or dates when the visitation may have been limited or flatly refused during that period of time.

Any meetings regarding staffing or documents that give us a record of training and orientation of staff if they work allocated within the facility are very helpful documentation, along with any furloughs and leaves of absence for providers who were concerned about contracting the disease are very important. Another thing that we recommend is maintaining a floor plan for how isolation is going to take place or did take place for patients that were COVID positive or suspected COVID positive, evidence of any in-service training for your staff, related specifically to the virus from this period of time. And any evidence of reviews of quality assurance or compliance would be a very helpful thing to maintain in terms of your record documentation. All of these things contribute to preserving memory. But then we also want to memorialize the people who really are your subject matter experts within your facility, about everything related to this crisis. So keep a record today of who was working in your HR department, and who is going to be your person with the most knowledge. If a deposition is taken during litigation later on, we want to not have to think back to who was working in 2020, we want to have that recorded. And that person may want to keep notes of what it was like to work during that period of time. And one final recommendation that we’ve made is, if possible, to have a video of the day in the life of your facility or your practice during this period of time. I think it is so important as memories fade, to get a context and to have a living example of how we functioned during this pandemic. Because hopefully, it will be but a distant memory a few years from now. And it will be important to be able to bring a jury back to this period in time and to really illustrate what it was like to deliver health care during a pandemic.

**ME: Does the typical malpractice insurance policy cover COVID-19-related claims?**

**Sheps:** It’s a little bit of a tricky question. Typically, yes, a medical professional liability policy covers what we call professional services, which is insurance company lingo for rendering medical care, essentially. So the policy would cover that. The exceptions come from the fact that most policies exclude willful or intentional conduct and many also exclude gross negligence. And unfortunately, because of the exceptions to most state immunities and federal immunity under the PREP Act, those exceptions are for willful misconduct or gross negligence, resulting in patient injury. The plaintiff’s attorneys are pleading the cases with those allegations to get around the immunity and the policy may not cover. Because of that, most carriers are going to look at things very fact specifically and look at it very critically with the allegation. And if there is an item of medical negligence that has been alleged, they will almost always defend the provider or facility under a reservation of rights, which essentially says, if this proves to be medical negligence and it is not been stopped by the immunity laws, we will cover this. If this truly becomes gross negligence or willful misconduct, then we will not be able to indemnify.”

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Transitional care management: Will changes make getting paid easier?

by Lisa A. Eramo, MA Contributing Author

Transitional care management (TCM) services, which help patients transition from inpatient care to the community setting, are critical for preventing readmissions and keeping patients on a smooth track to recovery. The services, denoted by CPT codes 99495 and 99496, also are lucrative for practices, paying up to approximately $248 for 30 days of service.

However, there’s one big challenge: Independent physicians aren’t usually notified when patients are admitted to and discharged from the hospital. This makes it difficult to meet TCM billing requirements that specify physicians must contact patients within two business days of discharge and conduct a follow-up visit within seven or 14 days post-discharge, depending on the patient’s medical complexity, says Samuel Leroy Church, M.D., CPC, family medicine physician in Hiawassee, Georgia, and an American Academy of Family Physicians adviser for the American Medical Association’s Current Procedural Terminology editorial panel.

The good news is that information between hospitals and physicians can flow more freely thanks to a new CMS Condition of Participation (CoP). CoPs are the health and safety standards that health care organizations must meet to participate in Medicare and Medicaid programs. The new CoP, which goes into effect May 1, 2021, requires hospitals (i.e., acute care hospitals, cancer hospitals, children’s hospitals, rehabilitation hospitals, long-term care hospitals and transplant programs) to send real-time e-notifications of any admissions, discharges or transfers (ADT) to applicable post-acute care providers with established care relationships who need that information for treatment, care coordination or quality-improvement activities.

E-notifications must include, at a minimum, the patient’s name, treating practitioner’s name and sending institution’s name. CMS created this
requirement as part of the Interoperability and Patient Access Final Rule (85 FR 25510) to significantly accelerate information sharing between hospitals and other providers across the care continuum.

“If hospitals routinely send us their information, it does eliminate a lot of steps and busywork on our part,” says Gregory Steinmetz, M.D., a family medicine physician in Warwick, Rhode Island. “It will be better for patient care, and primary care practices will have more incentives and support to provide TCM services.”

“If practices don’t already perform and bill TCM, they may want to consider it in light of these new changes,” says Peter S. Tippett, M.D., Ph.D., founder and CEO of careMESH, a technology platform that improves the quality and reach of ADT data from hospitals to physician practices. “If they already do, they may want to revisit the efficiency of their existing service line and explore ways to partner with local hospitals trying to satisfy the new CoP requirement.”

Experts provide these tips to create a successful TCM offering:

**Determine how the practice will receive ADT data**

The new CMS CoP is a big step forward because it means independent practices may start to receive this data automatically. However, in order for this process to occur seamlessly, patients will need to identify their primary care physician at the time of hospital registration, says Kim Huey, CPC, CCS-P, independent coding and reimbursement consultant in Alabaster, Alabama.

“This is a challenge because patients don’t seem to attach themselves to a primary care physician. Instead, they go to urgent care,” she says. “Care has become very fragmented.”

To address this challenge, physicians need to focus on building relationships with their patients, Huey says. Patients need to view their primary care as a one-stop shop for the majority of their health care needs. They also need to understand the importance of identifying their primary care physician when they are admitted to the hospital or seek care outside of the practice, she adds.

Another challenge with HIEs is that they are regional. If a practice belongs to one HIE and a patient is admitted to a hospital that is part of a different HIE, the practice won’t have access to ADT data.

HIEs aren’t necessarily a timely source of information either, says Cheryl Mongillo, MBA, administrative director at a family medicine practice in Wilmington, Delaware. Some hospitals don’t push their data to the HIE until physicians sign the discharge summary, she says. “It could take a week for this to happen, which means it’s beyond the window for billing TCM,” she adds.

Finally, ADT data exchange through HIEs only works if patients actually consent to participate in the HIE itself.

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Practices that belong to an Accountable Care Organization (ACO) may have more luck receiving timely ADT feeds. “What we pay to belong to our ACO has been worth it simply because it enables us to bill TCM,” Mongillo says. Her practice’s ACO sends ADT feeds for attributed patients as defined by their shared-savings contracts with Medicare, Medicaid and commercial payers. Then a medical assistant logs on to the ACO portal to check live data feeds and contact patients as necessary.

However, there are pitfalls even when receiving ADT feeds from an ACO. For example, when patients are discharged to a skilled nursing facility or inpatient rehabilitation facility, the ACO doesn’t have access to the facility name, making it difficult to track discharges from those settings, Mongillo says.

“Are there other patients who fall through the cracks? Absolutely because they may not be attributed to us, or we may not have a shared-savings contract with their insurer,” she says. However, there are other workarounds. For example, when patients come in for preoperative clearance, staff insert a flag in the EHR for the date of the surgery so they can follow up with the patient.

Mongillo also strives to build relationships with local hospitals so they provide ADT information via phone. “All hospitals have discharge planners,” she says. “I tell them, ‘Let us work with you to prevent readmissions. We can help schedule that follow-up visit to help the patient stay out of the hospital.’”

**Provide TCM via telehealth or home visits, when warranted**

If patients are unable to travel post-discharge, or if they are uncomfortable coming into the office during the pandemic, telehealth or home visits may be options. Giving patients the choice is paramount in terms of obtaining buy-in for TCM service, Mongillo says. “The more patients feel like they’re involved, the more willing they are to comply,” she adds.

Although Medicare covers TCM rendered via telehealth, commercial payer coverage may vary, says Huey, adding it’s best to contact each payer to determine its policy. Note
that Medicare and most other payers will also require modifier -95.

Identify other patient care needs and revenue opportunities

Chronic care management (CCM) is a big one. While TCM focuses on the 30 days post-discharge, CCM focuses on the patient’s health indefinitely, Church says. “It’s all part of an ongoing movement to centralize care in the primary care setting,” he adds.

Note that effective January 1, 2020, with the calendar year 2020 Physician Fee Schedule Final Rule, CMS relaxed its restrictions on concurrent use of TCM and CCM as long as the work is distinct, meaning both services address two different diagnoses. Previously, practices couldn’t bill TCM and CCM during the same 30-day period.

“This was an important step in reducing administrative worries for practices trying to run an ongoing CCM program aimed at long-term reduction of hospitalization and emergency room visits,” Church says. “You don’t necessarily need to abandon the CCM work in order to provide the TCM. That has been a big help.”

For example, a patient admitted to the hospital due to pneumonia can receive TCM upon discharge as well as CCM related to their diabetes and ulcers.

An annual wellness visit or advanced care planning are other billable services from which patients could also benefit at the time of TCM, Huey says.

Physicians also can separately bill an office visit at the time of TCM as long as documentation supports each code, Huey says. For example, a patient receiving TCM post-discharge after a hip replacement develops a sore throat and needs to be seen. Practices can bill the TCM and an E/M code during the same 30 days, Mongillo says.

“Many practices haven’t done this,” she adds. “This means they’ve been missing opportunities for revenue as well as closing care gaps.”

Ensure thorough documentation of TCM services

Physicians may be tempted to document TCM sparsely (“The patient is recovering well. I reconciled their medications and referred them for physical therapy,” for example). However, if the patient is readmitted or dies within 30 days, practices are obligated to change the visit from TCM to an office visit and resubmit a corrected claim, Huey says. That’s because TCM is technically for 30 days of service, she adds.

Huey recommends physicians document the TCM visit as they would any other office visit, just in case the visit does need to be rebilled. What diagnoses, if any, did the physician take into consideration when developing an ongoing treatment plan? This may include diagnoses in addition to the condition for which the patient was hospitalized. What is the assessment and plan?

“Even though all of those details may not be necessary to get the TCM paid, it’s going to show the complexity — everything you need to consider when treating the patient,” Huey says. This translates to more accurate E/M codes, particularly in 2021 when codes will be driven by medical decision-making or time.

If physicians aren’t already billing for TCM, they should strongly consider it as the industry moves toward a value-based care model, Church says. “TCM is not just about payment for providers or saving money for the system,” he adds. “It’s about patient care. Patient care is better. Quality of life is better. Patient engagement is better. Ultimately, care outcomes are better.”

“If practices don’t already perform and bill TCM, they may want to consider it in light of these new changes. If they already do, they may want to revisit the efficiency of their existing service line and explore ways to partner with local hospitals trying to satisfy the new CoP requirement.”

—Peter S. Tippett, M.D., Ph.D., founder and CEO, careMESH
Use apps to improve patient outcomes

by Keith A. Reynolds, Associate Editor

As the technological landscape evolves, so does the world of health care. Using smartphone apps, doctors can utilize technology to improve their understanding of their patients’ health.

While there are myriad apps available in digital storefronts hosted by Apple, Google and Amazon, it can be difficult to choose an effective app that also keeps patient health data safe.

The intelligence of smartphones in the exam room

Bradley Crotty, M.D., MPH, chief digital engagement officer and internist at Froedtert & Medical College of Wisconsin, sees the use of medical apps as a step along the road to making health care less of a transactional relationship between patient and physician.

“People come into the doctor’s office maybe two times a year, maybe four times a year, but most of the time they are managing their medical conditions along with their lives at home with their family,” he says. “They are left to take that 15 minutes or 30 minutes of time with a doctor and put together a plan, and then follow through with that plan at their home, at work or on the job.”

While these plans often consist of taking medication, they also may include changes in behaviors or routines that are more difficult for patients to engage with when they are not under their physician’s supervision.

Crotty says that smartphone medical apps and other digital tools can be a way for physicians to further patients’ health goals outside of the exam room by addressing behavior such as diet changes and exercise.

Choosing the right app

According to a 2016 study in Health Affairs, there were 165,000 mobile health apps available in Apple and Google digital storefronts. In the four years since that study was conducted, that number has only grown. According to IQVIA, over 200 health apps are added each day.

With a seemingly endless supply of possibilities to choose from, choosing one for patients can be daunting.

Crotty says that when creating a framework for deciding which apps to fold into a practice, keep in mind what goals there are for the app. Some apps are aimed solely at the patient, while some share information directly with the physician without the patient’s involvement. Complicating matters more, Crotty says some apps are a hybrid of the two.

It is also wise to assess whether any research has been done on the app, as many have not been approved by the U.S. Food and Drug Administration, according to Crotty.

The Health Affairs study suggests that clinicians and patients be included in the process of reviewing which apps to use. It found weak correlations between the consumer rating available on digital storefronts, their usability and their clinical utility.

Natasha Pufsina, M.D., practices internal and obesity medicine in Newark, New Jersey. She says that an often-overlooked aspect of choosing an app for patients to use is whether it is compatible with the practice’s EHR system.
An app may be perfect for a patient. “But how will that actually be implemented and integrated into the EHR?” she asks.

Another facet in deciding which apps is right for patients is cost. Apps that modify behavior and keep the patient in closer contact with their physician can ultimately save health care costs for both the patients and insurers, Crotty says.

Crotty believes that as these apps become more commonly used in a care setting, contracts with insurers likely will be negotiated to make the apps more economically viable as part of value-based care.

Apps may come with initial purchase costs or in-app-purchases, which can be a burden for patients, so that cost should also be taken into account when choosing which app patients should use.

Another facet addressed in the Health Affairs study is the apps’ crisis management. The authors found that the majority of apps they studied at the time were not equipped to properly deal with a situation where the data patients input indicate a health crisis.

Any app that tracks vital health information should be equipped with the ability to alert the doctor if a catastrophic health event is detected.

Privacy concerns
While these apps have many positive aspects, including improved accountability and ease of use, one of the biggest concerns regarding their use in the health care setting is the question of privacy.

The Health Affairs study found that many of the apps reviewed were using insecure data transfer methods, such as email and text messages, to pass information between the patient and physician.

Crotty says this is an issue that must be addressed as these apps become more prevalent in the health care space. He also is concerned about the lack of transparency by app developers who are known to sell user data.

He says that doctors should have a discussion with their patients, similar to an informal informed consent, about using these apps. Some of the questions that should be addressed include:

- What are the expectations for apps?
- If data are being transferred and reviewed, what are the expectations?
- How are the data being stored and how long are the data being kept?
- Where are the data being kept?

This conversation may be a patient’s best opportunity to receive direct answers to these questions, Crotty says.

Getting patients to use them
Fuksina finds it quite easy to get her patients to engage with apps due to the prevalence of similar technology in the market.

“Many people now own an [Apple Watch] or Fitbit are able to use their phones to download simple apps,” she says. “And even though we do not have, right now, an app [that] integrates with our particular EHR to be able to scale it ... it can ensure some patients’ responsibility and improve [adherence] and, in a way, help them be accountable for their own health goals. I’ve been able to inspire and teach them myself on several apps that I believe are very helpful.”

Crotty says to ask all patients what they are doing on their smartphones. It’s likely that they are already using their phones to search for health information on Google. Once that is known, a physician can look for opportunities to build on the what the patients are already using. To encourage patients to take full advantage of these apps, it’s important to get their families involved in keeping the patient accountable. “The patient and family are the least-utilized resource on a health care team,” Crotty says.
How physicians can humanize virtual care

In the 1930s, physician house calls represented 40 percent of all physician-patient encounters. By 1980, that number had fallen to less than one percent. But the “golden age” of the physician house call has come full circle—albeit in a virtual fashion.

With modern technology, not even the most welcoming office can humanize health care the way a virtual house call can. For years, we’ve assumed that physicians and patients must sit together in the same exam room to develop personal, trust-filled relationships. But COVID-19 has proven that communication technology can create enormously personal connections.

It’s easy to see why patients are eagerly embracing virtual relationships with their physicians as well. Eighty-three percent of Americans say they expect to make telehealth visits after COVID-19 has ended. This number is huge when you consider the fact that just eight percent of patients had ever had a telehealth visit before the pandemic hit. Many organizations put telehealth in place so quickly that they are struggling to live up to patient expectations when it comes to virtual communication. A recent study compared patient attitudes immediately prior to COVID-19 and then again months into the pandemic. It not only found that patients’ desire for digital communication has risen, but that overall patient satisfaction is down.

The good news is that the development of virtual relationships goes way beyond the traditional video or audio-based telehealth visit. In fact, the virtual physician-patient relationship can be built with or without the use of telehealth at all. There are a variety of ways practices can reach out to patients that don’t involve the actual visit.

Two-way texting
We all know that most people don’t answer incoming phone calls anymore. What you might be surprised to learn is that 19 percent of people never check their voicemail. Ever. This means that a huge number of those messages left by your staff are going ignored. Texting has become the most preferred way to communicate—and not just for friends and family. Forty-seven percent of patients (and this number is growing every day) want the ability to text back and forth with their provider. Two-way texting is the first step in developing a virtual relationship with patients. Patients are able to shoot off a quick text to ask a question or set up an appointment. You are able to respond quickly and easily.

Educational communication
Health care organizations should send out regular educational communication in the form of newsletters or emails. Much like the automated care instructions, this information will reinforce the feeling that you care about a patient’s health. This is especially important during times like COVID-19 where patients are feeling confused and worried. During the pandemic, always err on the side of over-communicating rather than under-communicating. In addition to regular newsletters, consider sending targeted educational information to patients who fall into specific categories. For example, you may want to send emails specifically to all of your patients over the age of 65 or those diagnosed with high-risk conditions such as diabetes.

Appointment and billing reminders
Did you know that the majority of patients fail to remember the recommendations and treatments their physicians give them? The use of automated calls or emails to remind patients of care instructions helps take care of this problem. At the same time, it lets patients know that you care about them and their health. Not only will this help improve care adherence rates, but it will also boost overall satisfaction levels. Patients feel connected to you and the relationship is strengthened.

Josh Weiner is the CEO of SR Health by Solutionreach. Send your practice management questions to Medec@mjhlifesciences.com.
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Battling COVID-19 with ‘digital vaccines’

As scientists endeavor to build biological vaccines for COVID-19, there is increasing recognition that societies must look beyond biological methods alone. This means “digital therapeutics,” are needed to change human behavior and build societal resilience.

In order to successfully combat the virus, we must complement biological vaccines with digital vaccines, a subcategory of digital therapeutics, to inform and educate the population and reinforce behavior.

Digital vaccines are envisioned as evidence-based prevention approaches delivered via smart phones and tablets to encourage positive behavior. They are gamified, digital interventions that draw on principles of neuroscience, psychology, artificial intelligence (AI) and behavioral economics to provide safe and low-risk mechanisms for influencing significant behavior change. The goal is to provide fun, immersive and motivational features within a mobile app to encourage nonaddictive, interactive, game-playing experiences and induce desired changes in behaviors.

This idea of digital health technologies is supported by the Food and Drug Administration (FDA). “In the context of the COVID-19 public health emergency, the use of digital health technologies...has the potential to facilitate social distancing by reducing patient contact with, and proximity to, health care providers, and can ease the burden on hospitals, other health care facilities and health care professionals that are experiencing increased demand due to the COVID-19 public health emergency,” the FDA reported in guidelines issued in April.

Digital vaccines can leverage proven neurocognitive training to change behaviors, reach a broad audience and be deployed widely, quickly and updated frequently. Using these training methods and mobile technologies, digital vaccines are showing promising evidence of changing behavior in pilot randomized controlled studies. Highly interactive video games with animation activities train the brain to improve processing, understanding and memory by stimulating the neurological functioning and the cognitive ability of individuals.

Digital vaccines that are enabled via gamified, mobile applications can be culturally sensitive and customizable to specific regions and contexts. They can entail deep levels of personalization to ensure that vaccines meet the requirements of target audiences from all geographical, social and cultural realms. For example, to develop a COVID-19 digital vaccine that promotes hand hygiene in a specific region in India, researchers are examining the sociological, environmental and regional norms to adapt an existing game for hand-hygiene literacy to include local preferences.

This technology would allow rapid deployment of the digital vaccine, which can learn and adapt based on live and forecasted data. In the case of a rapidly changing virus, we need to approach containment and immunization with agility and precision that exceeds the vectors of infection. AI-driven approaches provide a system of automated learning frameworks, moderated through human intervention and feedback loops, that can stay ahead of an epidemic.

We are in the process of adapting and scaling an existing digital vaccine, conducting randomized field trials and ongoing research and development to gather and analyze evidence of positive behavioral and physiological outcomes. We are working to design, implement and deploy the technology at scale within populations that are at high risk. The key outcomes will be tracking incidence of COVID-19, time factors and transmission rates, as well as uptake of health-hygiene practices.

If the trial is successful, this evidence-based digital vaccine candidate for infectious diseases could be made available for global adoption to help alleviate health challenges caused not only by COVID-19 but also infectious diseases to come.

Rema Padman, PhD, is Trustees Professor of Management Science and Healthcare Informatics at the Heinz College of Information Systems and Public Policy at Carnegie Mellon University in Pittsburgh.
You've controlled their A1c and blood pressure. But your patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) are still at risk.¹⁻³

**INFLAMMATION AND FIBROSIS**
ARE DESTROYING YOUR PATIENTS' KIDNEYS⁴

CKD PROGRESSION IN T2D IS INFLUENCED BY 3 MAJOR DRIVERS¹⁻⁴:

- **METABOLIC DRIVERS**
  - Elevated blood glucose (A1c) levels

- **HEMODYNAMIC DRIVERS**
  - Rise in blood pressure
  - High intraglomerular pressure

- **INFLAMMATORY AND FIBROTIC DRIVERS¹⁴**
  - Proinflammatory cytokines
  - Fibrotic proteins

Today, the treatment of CKD in T2D does not adequately address inflammation and fibrosis, a major driver of CKD progression⁴.

IT'S TIME TO EXPLORE AN UNADDRESSED DRIVER OF CKD IN T2D AT CKD-T2D.COM

3

Things You Should Know About Reversal of Direct Oral Anticoagulants

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This activity was written by PER® editorial staff under faculty guidance and review.

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The staff of PER® have no relevant financial relationships with commercial interests to disclose.

To learn more about this topic, including information on clinical indications for use of DOAC reversal agents, current guidelines for reversal therapies, and the roles of clinicians across the different disciplines, go to gotoper.com/online-cme-activities/cases-conversations/cac-doacrev2020

Release Date: December 1, 2020
Expiration Date: December 1, 2021

Learning Objectives
Upon successful completion of this activity, you should be better prepared to:

• Identify factors associated with high risk of severe bleeding in patients using direct oral anticoagulant (DOAC) therapy
• Evaluate the efficacy and safety of reversal agents for DOAC therapy

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The increased risk of bleeding is one of the most challenging adverse effects from using direct oral anticoagulants (DOACs), as this complication can be life threatening. DOACs (also called non-vitamin K oral anticoagulants, or NOACs) directly inhibit a specific clotting factor in the coagulation cascade. The DOACs are approved for the prevention of thromboembolic events, including deep vein thrombosis, pulmonary embolism and stroke prevention for patients with nonvalvular atrial fibrillation. Although rare, the reversal of anticoagulation may be indicated for patients with — or at risk for — serious or uncontrollable hemorrhage. Here are 3 things you should know about DOAC reversal.

**Prescribing a DOAC involves balancing the risk of life-threatening bleeding with the risk of thrombosis.**

Overall, the risk of major bleeding and intracranial hemorrhage (ICH) with DOACs is relatively small. The safety and efficacy profiles of DOACs are well established; compared to warfarin, DOACs are as effective or superior for the prevention of stroke and systemic embolism, with bleeding rates similar or lower to those of warfarin. The risk of bleeding is dependent on both individual patient characteristics and on anticoagulant-related factors, some of which are nonmodifiable. Patient-dependent risk factors include older age, non-White race, history of prior bleeding, comorbidities (e.g., liver disease, kidney disease, hypertension, diabetes, cancer and obesity), thrombocytopenia or bleeding disorder and concomitant antiplatelet medication. Anticoagulant-related risk factors include drug class, anticoagulant initiation and dose level.

Strategies to modify the risk of bleeding include addressing concomitant medications, comorbidities and alcohol misuse. Educating patients on their increased baseline risk and the signs and symptoms of bleeding for which they should seek medical attention can potentially improve adherence and outcome. In acute settings, the presence of one or more of the following factors can help identify a patient on a DOAC who is bleeding severely: hemodynamic instability, bleeding in a critical area, clinically evident bleeding with Hb decrease ≥2.0 g/dL or the need for ≥2 units PRBC.

**ID’ing Patients on DOACs With Severe Bleeding**

- Hemodynamic instability
- Bleeding in a critical area
- Clinically evident bleeding with Hb decrease ≥2.0 g/dL
- Need for ≥2 units PRBC

Hb, hemoglobin; PRBC, packed red blood cells

**Two agents are approved for reversing the anticoagulant effect of DOACs.**

Until several years ago, reversal of the anticoagulant effect of DOACs was a clinical challenge due to the limited availability of specific reversal agents. Idarucizumab is the first DOAC reversible agent to receive approval from the US Food and Drug Administration (FDA); it was approved for the reversal of dabigatran. Idarucizumab is a humanized murine monoclonal antibody fragment that binds to dabigatran with 350 times higher affinity than observed with native thrombin, thereby neutralizing its activity. In the phase 3 RE-VERSE AD trial, the administration of idarucizumab was evaluated in patients with uncontrollable bleeding (group A) and those undergoing an urgent procedure (group B). Of the patients in group A, 45.5% presented with gastrointestinal bleeding and 32.6% presented with ICH. The median time to hemostasis was 2.5 hours. In group B, 93.4% of patients with a median intended procedure time of 1.6 hours reached hemostasis. Mortality rates between the two groups were comparable (18.8% versus 18.9%).

Andexanet alfa is the first FDA-approved reversal agent for two DOACs: apixaban and rivaroxaban. This agent is a recombinant-modified human factor Xa decoy protein that binds to and reverses the effects of these two factor Xa inhibitors. Two clinical trials (ANNEXA-R and ANNEXA-A) investigated the reversal of rivaroxaban and apixaban, respectively. The ANNEXA-R trial included healthy volunteers receiving 20 mg of rivaroxaban daily. The results showed a reduction of anti-factor Xa activity of 92% compared to baseline, a statistically significant improvement compared with placebo ($P < .001$). No severe adverse events were reported, including the occurrence of thrombosis. Thrombin generation...
returned to pre-rivaroxaban levels.

Results from the ANNEXA-A trial demonstrated that andexanet was an effective reversal agent for apixaban. Anti-factor Xa activity was reduced by 94% among those who received andexanet ($P < .001$ compared with placebo). No major adverse events were reported, including no evidence of increased thrombosis. Thrombin generation was restored to pre-apixaban levels within 2 to 5 minutes of administration of andexanet.11

Ciraparantag is currently under investigation as a universal reversal agent for the anticoagulant effect of heparins (low molecular-weight heparin, unfractionated heparin) and DOACs (rivaroxaban, apixaban, dabigatran, betrixaban and edoxaban). Ciraparantag is a synthetic small, water-soluble molecule that binds to and blocks the effects of the above-mentioned agents.12 Recent data from two phase 2 clinical trials demonstrated that ciraparantag was well tolerated, and a single IV infusion rapidly reversed the anticoagulation in 83% to 100% of patients anticoagulated with apixaban or rivaroxaban in a dose-related manner.13

DOAC Reversal Agent Regulatory Status

3 DOAC reversal may be indicated in an emergency setting.

DOAC reversal agents have significantly changed the landscape of anticoagulant therapy in recent years. Prompt DOAC reversal can save lives but is also costly and potentially prothrombotic and should therefore be used only when indicated. According to recent guidelines from the Anticoagulation Forum regarding use of DOAC reversal agents, these are reserved for patients on DOACs who have life-threatening or critical organ bleeding or bleeding that is not responsive to maximum supportive measures, as well as patients on DOACs who are undergoing a procedure that cannot be performed safely during anticoagulation and cannot be delayed.14

DOAC Reversal Indications

- Life-threatening or critical organ bleeding not responsive to maximum supportive measures in patients on DOACs.
- Patients undergoing a procedure that cannot be performed safely during anticoagulation and cannot be delayed.

The occurrence of these clinical scenarios is rare. Additionally, specific guidelines have been published on DOAC reversal for the management of patients with acute ICH and patients after severe trauma.15,16

KEY REFERENCES


For a full list of references go to gotoper.com/go/doac2020print
**CME POST-TEST QUESTIONS**

1. When assessing the severity of bleeding, in addition to considering the site of bleeding and hemodynamic status of the patient, which of the following denotes the threshold drop in hemoglobin considered high risk for severe bleeding?
   - A ≥1 g/dL
   - B ≥1.5 g/dL
   - C ≥2 g/dL
   - D ≥2.5 g/dL

2. A 72-year-old man experiencing AF and rapid ventricular rate was admitted to the hospital, where he was successfully cardioverted and started on apixaban and metoprolol. Several months later, he fell and fractured his hip. The surgical team was concerned about operating emergently due to use of apixaban.

   What reversal agent can be recommended for this patient to reverse the effect of the specific direct oral anticoagulant agent?
   - A Andexanet alfa
   - B Ciraparantag
   - C Idarucizumab
   - D Prothrombin complex concentrates

3. A 69-year-old woman presents to the hospital with severe abdominal pain, and abdominal CT shows free air and a perforated colon. She has atrial fibrillation, diverticulitis and history of stroke 5 years ago. Her medications are dabigatran, atorvastatin and hydrochlorothiazide. A surgical consult advises urgent/emergent abdominal surgery.

   In addition to holding dabigatran, how should this patient be managed?
   - A Administer fresh frozen plasma
   - B Administer andexanet alpha
   - C Administer idarucizumab
   - D Provide supportive measures

To learn more about this topic, including information on clinical indications for use of DOAC reversal agents, current guidelines for reversal therapies and the roles of clinicians across the different disciplines, go to [gotoper.com/online-cme-activities/cases-conversations/cac-doacrev2020](http://gotoper.com/online-cme-activities/cases-conversations/cac-doacrev2020)
3

Things You Should Know About Hereditary Transthyretin (hATTR) Amyloidosis

Release Date: December 1, 2020
Expiration Date: December 1, 2021

Learning Objectives
Upon successful completion of this activity, you should be better prepared to:
• Recognize the varied phenotypic presentation and underlying genotypes of hereditary transthyretin (hATTR) amyloidosis
• Identify red-flag symptoms and the role of genetic testing methods in accurately diagnosing hATTR amyloidosis
• Evaluate the efficacy and safety of current and emerging agents for the treatment of patients with hATTR amyloidosis

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To learn more about this topic, including information on the genetic underpinnings, diagnostic approach and evidence-based treatment strategies, go to gotoper.com/online-cme-activities/online-activities/rdc-cn20

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This activity was written by PER® editorial staff under faculty guidance and review.

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Hereditary transthyretin (hATTR) amyloidosis is a rapidly progressive, degenerative and life-threatening disease caused by deposits of amyloid in cardiac, renal and nervous system tissues leading to disruption of organ structure and function. Patients with hATTR amyloidosis experience significant impairment in their quality of life (QOL). Although hATTR amyloidosis is a rare disease, greater access to genetic testing provides additional opportunity to form an accurate diagnosis. A positive family history of neuropathy or cardiomyopathy and multisystem involvement are red flags and should raise suspicion for this condition. Initiating prompt treatment can delay disease progression.

1. hATTR amyloidosis can present with a varied phenotype.

hATTR amyloidosis is one of multiple types of amyloidosis. It is a heterogenous, adult-onset condition inherited in an autosomal dominant manner, in which the genetic abnormality results in misfolding of the transthyretin (TTR) protein, which is synthesized and secreted by the liver. Worldwide, the prevalence of hATTR amyloidosis is approximately 50,000 cases. According to data from the Transthyretin Amyloid Outcomes Survey (THAOS), in which more than 34 mutations were reported, the most common are Val122Ile, Thr60Ala and Val30Met, with the most common in the United States being Val122Ile.

hATTR amyloidosis presents with a mixed phenotype influenced by geographic location, the environment and genetic factors. Symptoms can vary from a strictly cardiac presentation to a severe sensorimotor neuropathy with autonomic dysfunction, gastrointestinal complaints, compromised renal function and ocular manifestations. Even among patients with the same mutation from the same family, the phenotypic expression can vary.

<table>
<thead>
<tr>
<th>VARIANT MUTATION VARIANT</th>
<th>FOUND IN</th>
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<tr>
<td>Val30Met</td>
<td>Primarily individuals from Portugal, Spain, France, Sweden and Japan and descendants of people from these areas</td>
</tr>
<tr>
<td>Val122Ile</td>
<td>3% to 4% of African Americans and ≥ 5% of the population in some areas of West Africa</td>
</tr>
<tr>
<td>Thr60Ala</td>
<td>People of Irish descent; it is the most common variant present among those from the U.K.</td>
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2. Recognizing red-flag symptoms can help diagnose hATTR amyloidosis.

Patients with hATTR amyloidosis often present with a cluster of one or more red-flag symptoms: tingling/numbness in feet and/or hands, chronic gastrointestinal distress, bilateral carpal tunnel syndrome and/or heart failure.

- Tingling/numbness in feet or hands
- Chronic gastrointestinal distress
- Bilateral carpal tunnel syndrome
- Heart failure

Bilateral carpal tunnel syndrome in combination with progressive symmetric sensorimotor neuropathy and/or cardiomyopathy should raise suspicion of hATTR. The disease is confirmed by the detection of a mutation in the TTR gene via DNA sequencing or the presence of amyloid in tissue biopsy. The risk of misdiagnosis is a concern, as hATTR amyloidosis may not be considered in the differential diagnosis due to presence of overlapping and nonspecific symptoms. As a result, there can be a significant delay in diagnosis; a mean interval of 4 years from symptom onset to diagnosis has been observed for hATTR amyloidosis with polyneuropathy (hATTR-PN) and up to 8 years with hATTR amyloidosis with cardiomyopathy (hATTR-CM). Being aware of the red flags above can help improve recognition and enhance rates of accurate and timely diagnoses.

3. Novel therapies are available for hATTR amyloidosis.

Until several years ago, the only available treatment for hATTR amyloidosis was liver transplantation, but in the past decade, several medical therapies have been approved to delay disease progression. These therapies work via various mechanisms, notably stabilizing the TTR tetramer, and gene silencing, resulting in blocked TTR synthesis by hepatocytes.

**Stabilizing the TTR tetramer**

Tafamidis is a TTR stabilizer that slows down the progression of hATTR amyloidosis by restabilizing the TTR protein. It blocks tetramer dissociation, the rate-limiting step in the amyloidogenic process, and reduces the deposition of amyloid. Tafamidis shows benefit in patients with the Val30Met mutation, as well as other mutations, and is therefore a potential treatment for most patients with hATTR.
Early intervention with tafamidis led to minimal disease progression in patients with a mild form of ATTR-familial amyloid polyneuropathy (ATTR-FAP) for the duration of 5.5 years. Tafamidis has a clinical benefit for patients with heart failure related to ATTR-CM and received U.S. Food and Drug Administration (FDA) approval in this setting based on findings from the ATTR-ACT trial. In this trial, tafamidis-treated patients had fewer cardiovascular-related hospitalizations and lower all-cause mortality compared with placebo across all subgroups, with the exception of patients with NYHA class III heart failure. Tafamidis has an acceptable adverse effect profile, and the incidence and types of adverse events were similar for tafamidis- and placebo-treated patients.

Diffusil is a nonsteroidal anti-inflammatory drug and also acts as a TTR stabilizer. Diffusil improved QOL scores and reduced progression of neurological impairment compared with placebo in a randomized trial of patients with stage I-II ATTR-FAP. Currently, diffusil is not approved for hATTR amyloidosis but is sometimes used off-label. Diffusil has not been studied in a head-to-head fashion with tafamidis.

**Blocking hepatocyte synthesis of TTR through gene silencing**

TTR gene silencing therapy or RNA interference (RNAi) inhibits the production of TTR via deactivation of the TTR gene thereby preventing deposition of incorrectly folded transthyretin protein as ATTR-amyloid.

Patisiran, an RNAi therapeutic, may help promote clearance of TTR amyloid deposits in peripheral tissues and restore function to those tissues. Clinical trial data demonstrated significant improvement of neuropathy across the sensorimotor and autonomic domains. Patisiran treatment also resulted in significantly improved QOL, walking, nutritional status and activities of daily living. The FDA approved patisiran in 2018 for the treatment of adult patients with hATTR-PN. Long-term efficacy and safety data demonstrated a halt of rapid disease progression in patients who crossed over from placebo to patisiran. The most common adverse reactions are upper respiratory tract infections and infusion-related reactions. Patients should be monitored during infusion and required premedication should be administered at least 60 minutes prior to infusion.

Inotersen is an antisense oligonucleotide (ASO) inhibitor that selectively binds to mRNA that encodes for TTR, causing degradation of RNA responsible for producing TTR. As a result, synthesis of TTR protein is prevented, resulting in less TTR and a reduced rate of amyloid deposition. Inotersen significantly reduced neurological progression and improved health-related QOL at 8 and 15 months in patients with hATTR amyloidosis and polyneuropathy in the phase 3 NEURO-TTR trial. The FDA approved inotersen for the treatment of hATTR-PN in adults. Long-term efficacy and safety data demonstrated slowed disease progression and reduced deterioration of QOL in patients with hATTR-PN, with early initiation of treatment resulting in greater long-term disease stabilization than delayed initiation. Due to the risk of thrombocytopenia and glomerulonephritis, patients are required to receive laboratory testing prior to treatment, during treatment and for eight weeks after discontinuation of treatment.

**Investigational therapy**

Vutrisiran is an experimental RNAi therapeutic inhibiting the production of misfolded transthyretin by targeting and silencing faulty transthyretin mRNA. Currently, the safety and efficacy of vutrisiran versus placebo is being evaluated in ongoing phase 3 clinical trials as part of the international HELIOS study program. In 2020, vutrisiran received fast-track designation and orphan drug designation from the FDA for the treatment of polyneuropathy associated with hATTR amyloidosis based on positive results from a phase 1 trial.

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**KEY REFERENCES**


For a full list of references go to gotoper.com/go/hattr20print
CME POST-TEST QUESTIONS

1. What is the most common mutation present in patients with hATTR cardiac amyloidosis in the United States?
   A. Gly47Ala
   B. Phe64Leu
   C. Thr60Ala
   D. Val122Ile

2. Which of the following statements accurately describes a result of the ATTR-ACT trial conducted in patients with ATTR amyloid cardiomyopathy?
   A. Tafamidis had similar efficacy to diflunisal in slowing progression to heart failure
   B. Tafamidis showed reduction in all-cause mortality compared with placebo
   C. Tafamidis showed benefit over placebo in reducing cardiac-related hospitalizations only in patients with NYHA class III heart failure
   D. The incidence and severity of adverse events were higher in patients who received tafamidis than those who received placebo

3. An ongoing extension study evaluating the long-term efficacy and safety of patisiran in patients with hATTR amyloidosis and polyneuropathy showed which of the following outcomes?
   A. A decrease in serum TTR levels of approximately 80% at six months that lasted only an additional two months
   B. No improvement in health-related quality of life observed in any of the study cohorts
   C. Rapid disease progression was halted in most of the patients previously receiving placebo who crossed over to receive patisiran
   D. Common adverse reactions of muscle weakness, headache and elevation of liver transaminase levels

4. NEURO-TTR was a phase 3 study that evaluated the safety and efficacy of inotersen compared with placebo. Which of the following outcomes was seen in patients taking inotersen?
   A. Improvement in cardiomyopathy at six and 18 months
   B. Improvement in neuropathy at eight and 15 months
   C. A slight decrease in health-related quality of life at 12 months
   D. Prolonged survival at 36 months

To learn more about this topic, including information on the genetic underpinnings, diagnostic approach and evidence-based treatment strategies, go to gotoper.com/online-cme-activities/online-activities/rdc-cn20

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- Takes 10-15 minutes to prep patient, 20 minutes to test
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- Reimburses using 6 CPT codes, National Average = $750 - $1000 per test
- Each test is processed into a fully-finished, clinically actionable report
- Easy to understand biomarkers facilitate more informed medical interventions, such as biofeedback

ANS TESTING (can be combined with SUDOMOTOR into 1 full system)
- Takes less than 10 minutes to perform, software provides verbal cues
- Tests for autonomic balance, vascular health, physical/mental stress, peripheral nerve health and other critical hidden risk factors
- Reimburses $170/test using 3 CPT codes
- Provides a 1 page summary up to a full 24 page comprehensive report

SUDOMOTOR TESTING (can be combined with ANS into 1 full system)
- Takes 3 minutes to analyze a patient’s hands and feet
- Provides a 1 page summary report
- Assesses peripheral nerve health (c-fiber function) and asymmetry between each hand and foot
- Reimburses $130/test (national average)

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SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted)

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1 INDICATIONS AND USAGE

SHINGRIX is a vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older.

Limitations of Use:

SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

2 DOSAGE AND ADMINISTRATION

2.2 Administration Instructions

For intramuscular injection only.

After reconstitution, administer SHINGRIX immediately or store refrigerated between 2° and 8°C (36° and 46°F) and use within 6 hours. Discard reconstituted vaccine if not used within 6 hours.

2.3 Dose and Schedule

Two doses (0.5 mL each) administered intramuscularly according to the following schedule: A first dose at Month 0 followed by a second dose administered anytime between 2 and 6 months later.

4 CONTRAINDICATIONS

Do not administer SHINGRIX to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX [see Description (11) of full prescribing information].

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of SHINGRIX.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. There is the possibility that broad use of SHINGRIX could reveal adverse reactions not observed in clinical trials.

Overall, 17,041 adults aged 50 years and older received at least 1 dose of SHINGRIX in 17 clinical studies. The safety of SHINGRIX was evaluated by pooling data from 2 placebo-controlled clinical studies (Studies 1 and 2) involving 29,305 subjects aged 50 years and older who received at least 1 dose of SHINGRIX (n = 14,645) or saline placebo (n = 14,660) administered according to a 0- and 2-month schedule. At the time of vaccination, the mean age of the population was 69 years; 7,286 (24.9%) subjects were aged 50 to 59 years, 4,488 (15.3%) subjects were aged 60 to 69 years, and 17,531 (59.8%) subjects were aged 70 years and older. Both studies were conducted in North America, Latin America, Europe, Asia, and Australia. In the overall population, the majority of subjects were white (74.3%), followed by Asian (18.3%), black (1.4%), and other racial/ethnic groups (6.0%); 58% were female.

Solicited Adverse Events

In Studies 1 and 2, data on solicited local and general adverse events were collected using standardized diary cards for 7 days following each vaccine dose or placebo (i.e., day of vaccination and the next 6 days) in a subset of subjects (n = 4,886 receiving SHINGRIX, n = 4,881 receiving placebo with at least 1 documented dose). Across both studies, the percentages of subjects aged 50 years and older reporting each solicited local adverse reaction and each solicited general adverse event following administration of SHINGRIX (both doses combined) were pain (78.0%), redness (38.1%), and swelling (25.9%); and myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%), respectively.

The reported frequencies of specific solicited local adverse reactions and general adverse events (overall per subject), by age group, from the 2 studies are presented in Table 1.

Table 1. Percentage of Subjects with Solicited Local Adverse Reactions and General Adverse Events within 7 Daysa of Vaccination in Adults Aged 50 to 59 Years, 60 to 69 Years, and 70 Years and Olderb (Total Vaccinated Cohort with 7-Day Diary Card)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Aged 50-59 Years</th>
<th>Aged 60-69 Years</th>
<th>Aged ≥70 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHINGRIX %</td>
<td>Placebo%</td>
<td>SHINGRIX %</td>
<td>Placebo%</td>
</tr>
<tr>
<td>Local Adverse Reactions</td>
<td>n=1,315</td>
<td>n=1,312</td>
<td>n=1,311</td>
</tr>
<tr>
<td>Pain</td>
<td>88.4</td>
<td>14.4</td>
<td>82.8</td>
</tr>
<tr>
<td>Pain, Grade 3d</td>
<td>10.3</td>
<td>0.5</td>
<td>6.9</td>
</tr>
<tr>
<td>Redness</td>
<td>38.7</td>
<td>1.2</td>
<td>38.4</td>
</tr>
<tr>
<td>Redness, &gt;100 mm</td>
<td>2.8</td>
<td>0.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Swelling</td>
<td>30.5</td>
<td>0.8</td>
<td>26.5</td>
</tr>
<tr>
<td>Swelling, &gt;100 mm</td>
<td>1.1</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>General Adverse Events</td>
<td>n=1,315</td>
<td>n=1,312</td>
<td>n=1,300</td>
</tr>
<tr>
<td>Myalgia, Grade 3e</td>
<td>56.9</td>
<td>15.2</td>
<td>49.0</td>
</tr>
<tr>
<td>Fatigue, Grade 3</td>
<td>8.9</td>
<td>0.9</td>
<td>5.3</td>
</tr>
<tr>
<td>Fatigue, Grade 3d</td>
<td>57.0</td>
<td>19.8</td>
<td>45.7</td>
</tr>
<tr>
<td>Fatigue, Grade 3e</td>
<td>8.5</td>
<td>1.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Headache</td>
<td>50.6</td>
<td>21.6</td>
<td>39.6</td>
</tr>
<tr>
<td>Headache, Grade 3e</td>
<td>6.0</td>
<td>1.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Shivering</td>
<td>35.8</td>
<td>7.4</td>
<td>30.3</td>
</tr>
<tr>
<td>Shivering, Grade 3</td>
<td>6.8</td>
<td>0.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Fever</td>
<td>27.8</td>
<td>3.0</td>
<td>23.9</td>
</tr>
<tr>
<td>Fever, Grade 3</td>
<td>0.4</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>GIb</td>
<td>24.3</td>
<td>10.7</td>
<td>16.7</td>
</tr>
<tr>
<td>GI, Grade 3d</td>
<td>2.1</td>
<td>0.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Total vaccinated cohort for safety included all subjects with at least 1 documented dose (n).

a 7 days included day of vaccination and the subsequent 6 days.

b Data for subjects aged 50 to 59 years and 60 to 69 years are based on Study 1. Data for subjects 70 years and older are based on pooled data from Study 1: NCT01165177 and Study 2: NCT01165229.

Placebo was a saline solution.

Grade 3 pain: Defined as significant pain at rest; prevents normal everyday activities.

Grade 3 myalgia, fatigue, headache, shivering, GI: Defined as preventing normal activity.

Fever defined as >37.5°C/99.5°F for oral, axillary, or tympanic route, or >38°C/100.4°F for rectal route; Grade 3 fever defined as >39.0°C/102.2°F.

GI = Gastrointestinal symptoms including nausea, vomiting, diarrhea, and/or abdominal pain.

(continued on next page)
The incidence of solicited local and general symptoms was lower in subjects aged 70 years and older compared with those aged 50 to 69 years. The majority of solicited local adverse reactions and general adverse events seen with SHINGRIX had a median duration of 2 to 3 days. There were no differences in the proportions of subjects reporting any or Grade 3 solicited local reactions between Dose 1 and Dose 2. Headache and shivering were reported more frequently by subjects after Dose 2 (28.2% and 21.4%, respectively) compared with Dose 1 (24.4% and 13.8%, respectively). Grade 3 solicited general adverse events (headache, shivering, myalgia, and fatigue) were reported more frequently by subjects after Dose 2 (2.3%, 3.1%, 3.6%, and 3.5%, respectively) compared with Dose 1 (1.4%, 1.4%, 2.3%, and 2.4%, respectively).

Unsolicited Adverse Events

Unsolicited adverse events that occurred within 30 days following each vaccination (Day 0 to 29) were recorded on a diary card by all subjects. In the 2 studies, unsolicited adverse events occurring within 30 days of vaccination were reported in 50.5% and 32.0% of subjects who received SHINGRIX (n = 14,645) and placebo (n = 14,660), respectively (Total Vaccinated Cohort). Unsolicited adverse events that occurred in ≥1% recipients of SHINGRIX and at a rate at least 1.5-fold higher than placebo included chills (3.5% versus 0.2%), injection site pruritus (2.2% versus 0.2%), malaise (1.7% versus 0.3%), arthralgia (1.7% versus 1.2%), and dizziness (1.2% versus 0.8%).

Gout (including gouty arthritis) was reported by 0.18% (n = 27) versus 0.05% (n = 8) of subjects who received SHINGRIX and placebo, respectively, within 30 days of vaccination; available information is insufficient to determine a causal relationship with SHINGRIX.

Serious Adverse Events (SAEs)

In the 2 studies, SAEs were reported at similar rates in subjects who received SHINGRIX (2.3%) and placebo (2.2%) from the first administered dose up to 30 days post last vaccination. SAEs were reported for 10.1% of subjects who received SHINGRIX and for 10.4% of subjects who received placebo from the first administered dose up to 1 year post last vaccination. One subject (<0.01%) reported lymphadenitis and 1 subject (<0.01%) reported fever greater than 39°C; there was a basis for a causal relationship with SHINGRIX.

Optic ischemic neuropathy was reported in 3 subjects (0.02%) who received SHINGRIX (all within 50 days after vaccination) and 0 subjects who received placebo; available information is insufficient to determine a causal relationship with SHINGRIX.

Deaths

From the first administered dose up to 30 days post last vaccination, deaths were reported for 0.04% of subjects who received SHINGRIX and 0.05% of subjects who received placebo in 2 studies. Of 1,638 subjects who received placebo from the first administered dose up to 1 year post last vaccination, deaths were reported for 0.8% of subjects who received SHINGRIX and for 0.9% of subjects who received placebo. Causes of death among subjects were consistent with those generally reported in adult and elderly populations.

Potential Immune-Mediated Diseases

In the 2 studies, new onset potential immune-mediated diseases (pIMDs) or exacerbation of existing pIMDs were reported for 0.6% of subjects who received SHINGRIX and 0.7% of subjects who received placebo from the first administered dose up to 1 year post last vaccination. The most frequently reported pIMDs occurred with comparable frequencies in the group receiving SHINGRIX and the placebo group.

Dosing Schedule

In an open-label clinical study, 238 subjects 50 years and older received SHINGRIX as a 0- and 2-month or 0- and 6-month schedule. The safety profile of SHINGRIX was similar when administered according to a 0- and 2-month or 0- and 6-month schedule and was consistent with that observed in Studies 1 and 2.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of SHINGRIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

General Disorders and Administration Site Conditions

Decreased mobility of the injected arm which may persist for 1 or more weeks.

Immune System Disorders

Hypersensitivity reactions, including angioedema, rash, and urticaria.

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

For concomitant administration of SHINGRIX with inactivated influenza vaccine [see Clinical Studies (14.5) of full prescribing information].

7.2 Immunosuppressive Therapies

Immunosuppressive therapies may reduce the effectiveness of SHINGRIX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There are no available human data to establish whether there is vaccine-associated risk with SHINGRIX in pregnant women [see Use in Specific Populations (8.1) of full prescribing information].

8.2 Lactation

It is not known whether SHINGRIX is excreted in human milk. Data are not available to assess the effects of SHINGRIX on the breastfed infant or on milk production/excretion [see Use in Specific Populations (8.2) of full prescribing information].

8.5 Geriatric Use

Of the total number of subjects who received at least 1 dose of SHINGRIX in the 2 efficacy trials (n = 14,645), 2,243 (15.3%) were aged 60 to 69 years, 6,837 (46.7%) were aged 70 to 79 years, and 1,921 (13.1%) were 80 years and older. There were no clinically meaningful differences in efficacy across the age groups or between these subjects and younger subjects [see Clinical Studies (14.1, 14.2, 14.3) of full prescribing information]. The frequencies of solicited local and general adverse events in subjects aged 70 years and older were lower than in younger adults (aged 50 through 69 years) [see Adverse Reactions (6.1)].

17 PATIENT COUNSELING INFORMATION

• Inform patients of the potential benefits and risks of immunization with SHINGRIX and of the importance of completing the 2-dose immunization series according to the schedule.

• Inform patients about the potential for adverse reactions that have been temporally associated with administration of SHINGRIX.

• Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Storage:

Store vials of Lyophilized gE Antigen and Adjuvant Suspension Components refrigerated between 2° and 8°C (36° and 46°F). Protect vials from light. Do not freeze. Discard if the vials have been frozen.

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No matter how healthy they may feel, people aged ≥50 years are at risk for shingles.1-5 That’s why CDC recommends you vaccinate immunocompetent adults 50 years and older with SHINGRIX.6,*

The CDC Recommendations may help you identify patients for vaccination and establish protocols in your practice.

To read the full CDC Recommendations, visit us at RecoSHINGRIX.com

*ACIP recommendations adopted by CDC.
ACIP=Advisory Committee on Immunization Practices; CDC=Centers for Disease Control and Prevention.

Indication
SHINGRIX is a vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

Important Safety Information
• SHINGRIX is contraindicated in anyone with a history of a severe allergic reaction (eg, anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX
• Review immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of SHINGRIX
• Solicited local adverse reactions in subjects aged 50 years and older were pain (78.0%), redness (38.1%), and swelling (25.9%)
• Solicited general adverse reactions in subjects aged 50 years and older were myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%)
• SHINGRIX was not studied in pregnant or lactating women, and it is unknown if it is excreted in human milk. Therefore, it cannot be established whether there is vaccine-associated risk with SHINGRIX in pregnant women or if there are effects on breastfed infants or milk production/excretion
• Vaccination with SHINGRIX may not result in protection of all vaccine recipients

Please see Brief Summary of Prescribing Information for SHINGRIX on the previous pages.


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