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INDICATION

DYANAVEL™ XR (amphetamine) extended-release oral suspension is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including DYANAVEL XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

- DYANAVEL XR is contraindicated
  - In patients known to be hypersensitive to amphetamine, or other components of DYANAVEL XR. Hypersensitivity reactions, such as angioedema and anaphylactic reactions, have been reported
  - During treatment with monoamine oxidase inhibitors (MAOIs) and within 14 days following discontinuation of treatment with an MAOI because of the risk of hypertensive crisis

- Prior to and during treatment assess for the presence of cardiac disease. Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during DYANAVEL XR treatment.

- CNS stimulants can cause increases in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for tachycardia and hypertension.

- CNS stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Prior to treatment, assess for the presence of bipolar disorder.

- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients with ADHD. Monitor weight and height in children during treatment with DYANAVEL XR. Treatment may need to be interrupted in children not growing as expected.
Customize the **DYANAVEL XR** dose* to their responses and needs

*The starting dose is 2.5 or 5 mg, taken once-daily in the morning with or without food, may be titrated by 2.5 to 10 mg per day, every 4 to 7 days, up to a maximum dose of 20 mg per day. Periodically re-evaluate long-term use and adjust dosage as needed.

- Low starting dose options and the ability to titrate within one prescription¹
- Optimize the dose to balance symptom control and side effects
- Prior to treatment assess for cardiac disease and risk for abuse
- After prescribing, keep prescription records, educate about and monitor for abuse and overdose, and re-evaluate the need for DYANAVEL XR use

**If switching from other amphetamine products to DYANAVEL XR¹**
- To switch from another amphetamine product, discontinue treatment, then follow the titration schedule for DYANAVEL XR
- Do not substitute for other amphetamine products on a mg-per-mg basis because of different amphetamine base compositions and differing pharmacokinetic profiles

| CNS stimulants, including DYANAVEL XR, are associated with peripheral vasculopathy, including Raynaud’s phenomenon. Signs and symptoms are usually intermittent and mild; very rare sequelae include digital ulceration and/or soft tissue breakdown. Careful observation for digital changes is necessary during treatment with ADHD stimulants.
| Most common adverse reactions observed with amphetamine products: dry mouth, anorexia, weight loss, abdominal pain, nausea, insomnia, restlessness, emotional lability, dizziness, and tachycardia. There is limited experience with DYANAVEL XR in controlled trials. Based on this limited experience, the adverse reaction profile of DYANAVEL XR appears similar to other amphetamine extended-release products. The most common (≥2% in the DYANAVEL XR group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 108 patients with ADHD (aged 6–12 years) were: epistaxis (DYANAVEL XR 4%, placebo 0%), allergic rhinitis (4%, 0%) and upper abdominal pain (4%, 2%).
| DYANAVEL XR use during pregnancy may cause fetal harm.
| Breastfeeding is not recommended during treatment with DYANAVEL XR.

See Full Prescribing Information for complete Dosing and Administration.

**Please see additional Important Safety Information, including Boxed Warning regarding potential for Abuse and Dependence, and Brief Summary of Full Prescribing Information on next page.**

DYANAVEL™ XR (amphetamine) extended-release oral suspension, CII 2.5 mg/mL

BRIEF SUMMARY: See Full Prescribing Information for complete product information.

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CNS stimulants, including DYANAVEL XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

INDICATIONS AND USAGE
DYANAVEL XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

CONTRAINDICATIONS
DYANAVEL XR is contraindicated: in patients known to be hypersensitive to amphetamine, or other components of DYANAVEL XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions were reported in patients treated with other amphetamine products. During treatment with MAOIs, and also within 14 days of discontinuation of treatment with a MAOI, because of risk of hypertensive crisis.

WARNING AND PRECAUTIONS
Potential for Abuse and Dependence (See Boxed Warning above). Serious Cardiovascular Reactions: Sudden death, stroke, myocardial infarction were reported in adults with CNS stimulant treatment at recommended doses. Sudden death reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during DYANAVEL XR treatment.

Blood Pressure / Heart Rate Increases: CNS stimulants cause increase in blood pressure (mean increase ~2-4 mm Hg) and heart rate (mean increase ~3-6 bpm). Monitor for potential tachycardia and hypertension.

Psychiatric Adverse Reactions: Elevation of Preexisting Psychotic CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with preexisting psychotic disorder. Induction of a Manic Episode in Patients with Bipolar Illness: CNS stimulants may induce mixed or manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk for developing a manic episode. New Psychotic or Manic Symptoms: CNS stimulants, at recommended doses, may cause psychotic or manic symptoms in patients without prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing DYANAVEL XR. In pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in 0.1% of CNS stimulant-treated compared to 0% in placebo-treated patients.

Long-Term Suppression of Growth: CNS stimulants were associated with weight loss and slowing growth rate in pediatric patients. Closely monitor growth (weight, height) in pediatrics treated with CNS stimulants, including DYANAVEL XR.

Peripheral Vasculopathy, including Raynaud’s Phenomenon: Stimulants, including DYANAVEL XR are associated with peripheral vasculopathy, including Raynaud’s phenomenon. Signs, symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects were observed in post-marketing reports at different times, therapeutic doses in all age groups through treatment. Signs, symptoms generally improve after dose reduction or discontinuation of drug. Careful observation for digital changes is necessary during treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

ADVERSE REACTIONS
Clinical Trial Experience: Because clinical trials are conducted under varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect rates observed in clinical practice. With Other Amphetamine Products in Pediatric Patients and Adults with ADHD: Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There were isolated reports of cardiomyopathy associated with chronic amphetamine use. CNS Psychotic episodes at recommended doses, overdose stimulation, restlessness, irritability, euphoria, dyskinesia, dysphoria, depression, tremor, tics, aggression, anger, ligernea, insomnia, emotional liability and dizziness. Eye Disorders: Vision blurred, mydriasis. Gastrointestinal: Dryness of mouth, unpleasant taste, diarrhea, constipation, nausea, other gastrointestinal disturbances. Anorexia, weight loss may occur as undesirable effects. Allergic: Urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis were reported. Endocrine: Impotence, changes in libido, Skin: Alopecia. With DYANAVEL XR in Pediatric Patients with ADHD There is limited experience with DYANAVEL XR in controlled trials. Based on this, the adverse reaction profile of DYANAVEL XR appears similar to other amphetamine extended-release products. Most common (≥2% DYANAVEL XR group and greater than placebo) adverse reactions reported in Phase 3 controlled study conducted in n=108 with ADHD (aged 6–12 yrs) were: epistaxis, allergic rhinitis, upper abdominal pain.

Table 1. Common Adverse Reactions Occurring in ≥2% of Subjects on DYANAVEL XR & greater than Placebo during double blind phase.

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>DYANAVEL XR (N=52)</th>
<th>Placebo (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Rhinitis allergic</td>
<td>3.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>3.8%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

Postmarketing Experience
Adverse reactions were identified during post approval of other amphetamine products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate frequency or establish causal relationship to drug exposure. Endocrine: frequent or prolonged erections. Musculoskeletal, Connective Tissue, and Bone Disorders: rhabdomyolysis. Psychiatric Disorders: delirium.

DRUG INTERACTIONS
Drugs Having Clinically Important Interactions with Amphetamines MAOI: MAOI antidepressants slow amphetamine metabolism, increasing amphetamine effect on release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results. Intervention: Do not administer DYANAVEL XR during or within 14 days following administration of MAOI. MAOI, MAOI, MAOI, MAOI. Concomitant use should be avoided. Acetylcysteine: Lower blood levels and efficacy of amphetamines. Intervention: Increase dose based on clinical response. Tricylic Antidepressants: May enhance activity of tricylic or sympathomimetic agents causing striking and sustained increases in concentration of d-amphetamine in brain; cardiovascular effects can be potentiated. Intervention: Monitor frequently, adjust or use alternative therapy based on clinical response. Potent Pump Inhibitors: Time to maximum concentration (Tmax) of amphetamine is increased compared to when administered alone. Intervention: Monitor patients for changes in clinical effect, adjust therapy based on clinical response.

Drug/Laboratory Interactions: Amphetamines can cause elevation in plasma corticosteroids. This is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

USE IN SPECIFIC POPULATIONS
Pregnancy: Risk Summary - There are limited published data on amphetamines in pregnant women. Data are insufficient to determine drug-associated risk of major congenital malformations or miscarriage. Adverse pregnancy outcomes, including premature delivery, low birth weight, in infants born to mothers dependent on amphetamines. DYANAVEL XR may cause fetal harm. Lactation: Risk Summary - There are limited case reports in published literature, amphetamine (d- or d, l-) is present in human milk, at relative infant doses of 2%-13.8% of maternal weight-adjusted dosage and milk/plasma ratio ranging 1.9 to 7.5. Because of potential for serious adverse reactions in breastfed infant, advise patients breastfeeding is not recommended during treatment with DYANAVEL XR.

Pediatric Use: Safety and effectiveness were established in patients with ADHD ages 6-17. Safety and efficacy in patients younger than 6 yrs with ADHD have not been established.

Geriatric Use: DYANAVEL XR has not been studied in geriatrics.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: DYANAVEL XR contains amphetamine, which is a Schedule II controlled substance in the U.S. Controlled Substance Act.

OVERDOSAGE
Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdose. Individual patient response varies widely. Toxic symptoms may occur idiosyncratically at low doses. Manifestations of overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow CNS stimulation. Others include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, abdominal cramps. Fatal poisoning usually preceded by convulsions and coma. Manufactured by: Tris Pharma, Inc., Monmouth Junction, NJ 08852 www.trispharma.com Based on LB 4147, Rev02

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**INDICATION**

EMVERM (mebendazole) 100 mg chewable tablet is indicated in adults and children over 2 years of age for the treatment of Enterobius vermicularis (pinworm) and Ascaris lumbricoides (common roundworm), Ancylostoma duodenale (common hookworm), and Necator americanus (American hookworm) in single or mixed infections.

**IMPORTANT SAFETY INFORMATION**

Mebendazole is contraindicated in persons who have shown hypersensitivity to the drug.

**Warnings:** There is no evidence that mebendazole, even at high doses, is effective for hydatid disease. There have been rare reports of neutropenia and agranulocytosis when mebendazole was taken for prolonged periods and at dosages substantially above those recommended.

**Precautions:** Periodic assessment of organ system functions, including hematopoietic and hepatic, is advisable during prolonged therapy.

**Adverse reactions include:** Transient symptoms of abdominal pain and diarrhea with expulsion of worms in cases of massive infection; liver function test elevations [AST (SGOT), ALT (SGPT), and GGT]; and on rare occasions hypersensitivity (rash, urticaria and angioedema); rare reports of neutropenia, agranulocytosis (see Warnings) and hepatitis when mebendazole was taken for prolonged periods and at dosages substantially above those recommended; and very rare cases of convulsions.

**Drug Interactions:** Preliminary evidence suggests that cimetidine inhibits mebendazole metabolism and may result in an increase in plasma concentrations of mebendazole.

**INDICATION**

EMVERM (mebendazole) 100 mg chewable tablet is indicated in adults and children over 2 years of age for the treatment of Enterobius vermicularis (pinworm), Trichuris trichiura (whipworm), Ascaris lumbricoides (common roundworm), Ancylostoma duodenale (common hookworm), and Necator americanus (American hookworm) in single or mixed infections.

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**Drug Interactions:** Preliminary evidence suggests that cimetidine inhibits mebendazole metabolism and may result in an increase in plasma concentrations of mebendazole.
EMVERM™ (mebendazole) 100 mg Chewable Tablets

BRIEF SUMMARY: See Package Insert for full prescribing information

INDICATIONS AND USAGE
Mebendazole tablets are indicated for the treatment of Enterobius vermicularis (whipworm), Trichuris trichuria (whipworm), Ascaris lumbricoides (common roundworm), Ancylostoma duodenale (common hookworm), Nectator americanus (American hookworm) in single or mixed infections. Efficacy varies as a function of such factors as preexisting diarrhea and gastrointestinal transit time, degree of infection, and helminth strains. Efficacy rates derived from various studies are shown in the table below.

<table>
<thead>
<tr>
<th></th>
<th>Pinworm (enterobiasis)</th>
<th>Whipworm (trichuriasis)</th>
<th>Common Roundworm (ascariasis)</th>
<th>Hookworm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure rates mean</td>
<td>95%</td>
<td>68%</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>Egg reduction mean</td>
<td>—</td>
<td>93%</td>
<td>99%</td>
<td>99%</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS
Mebendazole is contraindicated in persons who have shown hypersensitivity to the drug.

WARNINGS
There is no evidence that mebendazole, even at high doses, is effective for hydatid disease. There have been rare reports of neutropenia and agranulocytosis when mebendazole was taken for prolonged periods and at dosages substantially above those recommended.

PRECAUTIONS
General
Periodic assessment of organ system functions, including hematopoietic and hepatic, is advisable during prolonged therapy.

Information for Patients
Patients should be informed of the potential risk to the fetus in women taking mebendazole during pregnancy, especially during the first trimester (See Pregnancy Category C).

Children
Preliminary evidence suggests that cimetidine inhibits mebendazole metabolism and may result in an increase in plasma concentrations of mebendazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In carcinogenicity tests of mebendazole in mice and rats, no carcinogenic effects were seen at doses as high as 40 mg/kg (one to two times the human dose, based on mg/m²) given daily over two years. Dominant lethal mutation tests in mice showed no mutagenicity at single doses as high as 640 mg/kg (18 times the human dose, based on mg/m²). Neither the spermatocyte test, the F₂ translocation test, nor the Ames test indicated mutagenic properties. Doses up to 40 mg/kg in mice (equal to the human dose, based on mg/m²), given to males for 60 days and to females for 14 days prior to gestation, had no effect upon fetuses and offspring, though there was slight maternal toxicity.

Pregnancy
Teratogenic Effects
Pregnancy Category C
Mebendazole has shown embryotoxic and teratogenic activity in pregnant rats at single oral doses as low as 10 mg/kg (approximately equal to the human dose, based on mg/m²). In view of these findings the use of mebendazole is not recommended in pregnant women. Although there are no adequate and well-controlled studies in pregnant women, a postmarketing survey has been done of a limited number of women who inadvertently had consumed mebendazole during the first trimester of pregnancy. The incidence of spontaneous abortion and malformation did not exceed that in the general population.

In 170 deliveries on term, no teratogenic risk of mebendazole was identified.

Nursing Mothers
It is not known whether mebendazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mebendazole is administered to a nursing woman.

Pediatric Use
The drug has not been extensively studied in children under two years; therefore, in the treatment of children under two years the relative benefit/risk should be considered.

ADVERSE REACTIONS
Gastrointestinal
Transient symptoms of abdominal pain and diarrhea in cases of massive infection and expulsion of worms.

Hypersensitivity
Rash, urticaria and angioedema have been observed on rare occasions.

Central Nervous System
Very rare cases of convulsions have been reported.

Liver
There have been liver function test elevations [AST (SGOT), ALT (SGPT), and GGT] and rare reports of hepatitis when mebendazole was taken for prolonged periods and at dosages substantially above those recommended.

Hematologic
Neutropenia and agranulocytosis. (See WARNINGS).

OVERDOSAGE
In the event of accidental overdosage, gastrointestinal complaints lasting up to a few hours may occur. Vomiting and purging should be induced. Activated charcoal may be given.

DOSAGE AND ADMINISTRATION
The same dosage schedule applies to children and adults. The tablet may be chewed, swallowed, or crushed and mixed with food.

<table>
<thead>
<tr>
<th></th>
<th>Pinworm (enterobiasis)</th>
<th>Whipworm (trichuriasis)</th>
<th>Common Roundworm (ascariasis)</th>
<th>Hookworm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1 tablet, once</td>
<td>1 tablet morning and evening for 3 consecutive days</td>
<td>1 tablet morning and evening for 3 consecutive days</td>
<td>1 tablet morning and evening for 3 consecutive days</td>
</tr>
</tbody>
</table>

If the patient is not cured three weeks after treatment, a second course of treatment is advised. No special procedures, such as fasting or purging, are required.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. To report SUSPECTED ADVERSE REACTIONS contact Impax Laboratories, Inc. at 1-877-994-6729.


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The Addict Next Door

She was the doted-on only child of college-educated parents living in a comfortable Cleveland, Ohio, suburb with leafy tree-lined streets. She made all her well-child visits, never missed an inoculation, had good grades in school—and a treasured goldfish collection.

But the lure of OxyContin on the streets to which her peer group led her at age 18 ended in a full-blown heroin addiction when the pusher’s pills became more expensive than the blow.

My colleague’s daughter’s years in addiction hell continued through to still more addictive pills on the pretext of recovery. Suboxone became her new Oxy, with prescriptions written by a local physician who himself, it turned out, was addicted to heroin.

Will you pledge?

On August 26, US Surgeon General Vivek Murthy, MD, sent a letter to all US physicians imploring them to take a more active role in stemming the opioid crisis. He closed it by asking you and your peers to sign a 3-pronged online pledge:

1. First, to educate yourself on how to safely and effectively treat pain.
2. Second, to screen your patients for opioid use disorder and provide or connect them with evidence-based treatment.
3. And finally, to discuss and treat opioid addiction as the chronic illness it is—not a moral failing.

“‘We, as clinicians, are uniquely positioned to turn the tide on the opioid epidemic.’”
—US Surgeon General Vivek Murthy, MD, MBA

The days of some remote crisis striking some edge of society that one only encounters on the police blotter or at the homeless shelter are over. These are the children in your waiting room right now.

Have you lost a patient or former patient to opioid overdose?

Source: Contemporary Pediatrics online poll, August 2016

30% NO
70% YES

Our special opioid coverage starts on page 10.

Turn the Tide

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Turn the Tide

30% NO
70% YES

Our special opioid coverage starts on page 10.
Opioid abuse leads to more ED visits

From 2006 to 2012, patients aged younger than 18 years made more than 21,928 visits to emergency departments (EDs) for poisoning by prescription opioids, such as methadone, codeine, meperidine, or morphine. According to an analysis of data from the Nationwide Emergency Department Sample, about 62% of these visits were for unintentional overdoses, with the remaining proportion for intentional abuse, either for recreational purposes or for self-harm. Although patients were distributed almost equally between sexes, significantly more females than males were treated for intentional overdoses (31.2% vs 16.8%, respectively). And, not surprisingly, most visits in the youngest age group (0-5 years) were for unintentional overdoses, while those in the adolescent age group (15-17 years) were largely intentional.

About 65% of youngsters with unintentional poisonings were released from the ED after treatment, whereas patients with intentional poisoning were far more likely to be admitted. A total of 11 patients died, and 39 required mechanical ventilation (Tadros A, et al. Am J Drug Alcohol Abuse. 2016;42[5]:550-555).

Identify food insecurity in hospitalized kids

About one-quarter of children who recently have been hospitalized live in food insecure households, which suggests that hospitalization presents a potential opportunity to identify these youngsters and help their families access nutrition assistance.

Using data from the National Health and Nutrition Examination Survey, 2007 to 2012, for children and adolescents aged through 19 years (a total of 12,627 individuals), investigators analyzed parental responses to a questionnaire designed to measure household food security during the preceding 12 months.

The questionnaire consisted of 18 queries; households that answered “yes” to 3 or more of the queries were considered food insecure. As part of the survey, respondents also were asked if their child had been a patient in a hospital overnight in the past 12 months and if any member of the household had received Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) benefits or were enrolled in the Supplemental Nutrition Assistance Program (SNAP)—food stamps.

Of the 706 recently hospitalized children, 25.3% overall lived in food insecure households, with higher prevalence in recently hospitalized girls, non-Hispanic black children, Hispanic children, those of other

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commentary

It should not be a surprise that increasing recreational use of opioids has led to a spike in ED visits among those who use the drugs. It is good to remember, however, that having more households containing opioids leads to having more accidental ingestions, especially among young children in these homes.

—Michael G Burke, MD

FAST FACT

Prevalence of food insecurity was 38% among hospitalized, low-income children.
Fecal *Bacteroides* are linked to bronchiolitis

Investigators identified 4 distinct fecal microbiota profiles in infants hospitalized with bronchiolitis and found that 1 of those profiles—dominated by *Bacteroides*—was associated with a higher likelihood of bronchiolitis than the others.

The case control study was conducted in 40 infants aged younger than 12 months who were hospitalized for bronchiolitis in 1 of 3 facilities, and 115 healthy infants. Median age overall was 3 months. Investigators collected fecal samples from all participants and used gene sequencing to determine the relative abundance of various organisms. In addition to the *Bacteroides*-dominant profile, they identified profiles dominated by *Escherichia*, *Bifidobacterium*, and *Enterobacter/Veillonella*.

The proportion of infants with severe bronchiolitis was lowest (15%) in the *Enterobacter/Veillonella*-dominant profile compared with highest (44%) in the *Bacteroides*-dominant profile—a significant difference. However, the likelihood of bronchiolitis in infants with the *Escherichia*-dominant or *Bifidobacterium*-dominant profile was not significantly different than in those with the *Enterobacter/Veillonella*-dominant profile. These findings persisted after adjustment for variables (Hasegawa K, et al. Pediatrics. 2016;138[1]:e20160218).

**commentary**

Investigators are making more and more interesting observations on the microbiome. In this case, it is not clear if variation in the fecal flora causes more severe respiratory viral infections and bronchiolitis. However, the researchers suggest that gut microbiota dominated by certain bacteria, in this case *Bacteroides*, “attenuates the development of the immune function in the respiratory tract and thereby leads to an increased susceptibility to bronchiolitis.” They cite other studies to support this theory. We still have lots to learn about how we interact with organisms on us and in us. —Michael G Burke, MD
Opioids
A pediatric epidemic

Dr Bass is chief medical information officer and associate professor of medicine and of pediatrics, Louisiana State University Health Sciences Center–Shreveport. The author has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

Pediatricians may not recognize the growing problem of opioid abuse in their communities. As a result, physicians need to carefully examine their prescribing practices.

PAT F BASS III, MD, MS, MPH

Opioid use is now a significant problem for the pediatrician and the families served in pediatric practices. Whereas patients with a prior history of drug use, misuse, or suspicions of drug misuse have long been studied, monitored, screened, and treated for adverse outcomes, opioid-naïve patients with legitimate medical reasons for opioid prescriptions may represent a greater risk for opioid complications.

Although marijuana and alcohol abuse are declining, abuse of prescription opioids has more than doubled.1 Prescription opioids were second only to marijuana for 2.2 million adolescent first-time users of an illicit drug in 2009.2

Pediatric providers may be dispensing more opioids than are needed and contributing to the nonmedical use of opioids.3,4

One of the major concerns is that compared with other drugs of abuse among adolescents, the temporal progression from initiation to addiction among opioids is both common and accelerated.5 This article will review a number of concepts and problems as well as provide some practical pointers for dealing with opioids in a busy office practice.

Description of the problem
Failing grades, changes in friends, changes in appearance, discipline problems, legal problems, social problems, or overdose represent the myriad of ways that an opioid use disorder may present to the pediatric practice. Frighteningly for both parents and the pediatrician, opioid use disorder can present as a fatal event in the absence of dependence, family knowledge of a problem, or even with first use.5 Although

1800
Morphine is first isolated from opium.

1832
Codeine is the second opiate alkaloid to be isolated from opium.

1874
Chemists trying to find a less addictive form of morphine create heroin, which has twice the potency of morphine.
many pediatricians might not think this issue impacts their practice, the following statistics point out that there are probably very few pediatric practices not impacted by this growing epidemic:

- Unaware of the risks of nonmedical opioid use, most adolescents misusing opioids receive them free from a friend or relative.6
- Opioid prescriptions to adolescents and young adults nearly doubled from 1994 to 2007.7
- In 2014, there were more than 460,000 adolescents who were current nonmedical users of pain relievers, and 168,000 had an addiction to prescription pain relievers.8
- In 2014, 28,000 adolescents used heroin in the prior year and 16,000 were current users.8
- In 2013, 169,000 adolescents and young adults used heroin for the first time.9
- In 2009, 1.2% of high school students self-reported heroin use at least once.2
- In 2011, nearly 9% of high school seniors illegally used nonmedical prescription opioids in the last year,10 with a 13% incidence of lifetime use.11
- The socioeconomic status of pediatric patients beginning nonmedical use of opioids is increasing.5
- Drug overdose death rates have increased more than 250% since 2001, with much of the increase attributed to opioids.5
- In New York City, unintentional opioid overdose deaths increased from 59 to 220 between 2000 and 2011.12
- More boys seek treatment for heroin abuse compared with girls, but girls are more likely to be injection users.5
- Forty percent to 90% of adolescent opioid abusers will transition to heroin use.5
- Whereas more recent reports find a decline in the nonmedical use of opioids among pediatric patients, heroin is also being used at a much younger age.

**Where do kids get opioids?**

Opioids are relatively easy to get given the extent to which they are prescribed in the United States today. Adolescents often need to go no further than a nearby handbag, kitchen counter, or medicine cabinet—a drug dealer is not required.5

Adult prescriptions of opioids increasingly are noted to be related to adolescent exposures resulting in emergency department visits, hospitalization, and death. Following the Joint Commission emphasis on pain control and subsequent increase of opioid prescriptions of more than 300% beginning in 2000, both the number and severity of adolescent opioid-related events reported to poison control centers increased significantly.13 Among adolescents, this is more likely to represent intentional use (eg, recreational or intent for self-harm) compared with younger pediatric patients for whom accidental ingestion is more likely.14

Opioids are also increasingly prescribed to adolescents, potentially excessively. In a large study of pain medication scripts issued after a tooth extraction, a 3-fold difference was noted in the morphine equivalents between the 10th and 90th percentiles for a given procedure. This would suggest that at least...
some patients are being prescribed opioids excessively. Of particular concern in this study, patients aged between 14 and 17 years and 18 to 24 years had the highest percentage of filled prescriptions. Other studies have demonstrated increased risk of recurrent and increasing dosages, opioid use among patients believed to have relatively minor medical problems, and opioids prescribed legitimately.

Do kids understand the risks?

Despite wide media and medical reporting of the increasing problems of prescription opioids, adolescents may not be aware of or understand the risks. Much of the literature describing high-risk populations specifically targets the young adult (eg, those aged 18 to 25 years) so the adolescent population could be thought of as even less knowledgeable and less prepared.

Because opioids are prescribed by physicians, these drugs are legal and regulated by governments. Nonmedical use of prescription opioids often is not recognized as potentially harmful and may even be viewed as harmless, especially compared with drugs such as heroin. In general, these prescription drugs are also viewed as socially acceptable. This is further supported by popular beliefs that associate heroin as a “dangerous street drug” and prescription opioids not being associated with such a negative cultural narrative.

Adolescents may also have the misbelief that prescription opioids are safer than heroin, and that non-injection routes of administration are associated with less risk of overdose compared with injection routes. As a result of these misbeliefs, adolescents may be more likely to overdose from prescription opioids because they underestimate the potency of the drug they are using and they see their use as very different from what they consider to be street users. Additionally, knowledge regarding factors that increase risk of overdose, preventing overdose, and addressing an overdose when it occurs are limited. Further, there is a great deal of misinformation and lack of understanding related to overdose risk and polysubstance use among nonmedical users of opioids. Similarly, few nonmedical users of opioids are familiar with naloxone or its appropriate use for treating opioid overdose.

Other beliefs impact young adults’ decisions and actions related to opioids. Many young adults see very clear differences between nonmedical users of prescription opioids and persons they view as “junkies.” There is a perception among this group that heroin users are low income and more severely addicted despite opioid addiction being highest among white males and increasingly being associated with higher socioeconomic status. In fact, prevalence of drug misuse is actually low among minority adolescents and a great deal of current research is focusing on identifying protective factors. Interestingly, these beliefs persist among nonmedical users of prescription opioids who transition to heroin use.

Which kids are at risk?

Estimates of the genetic component of addiction risk range from 40% to 60%, and the thought is that the
risk applies equally across all substances. Although there is some discussion of genetic testing to guide treatment in chronic pain treatment among adults, this author could find no recommendation for genetic testing to determine risk among adolescent patients.

Environmental risk factors can increase risk generally or specifically for opioids. Stress and exposure to drug use among family or friends are thought to generally increase addiction risk. Depression, anxiety, and other comorbid psychiatric disorders also increase risk. Developmental vulnerabilities such as excitement seeking, extreme extroversion, and impulsivity generally increase the risk for adolescents to addiction. Access to opioids, through either appropriate medical use or nonmedical use, as well as permissive attitudes toward opioids are more specific risk factors for opioid addiction. Cheaper prices of heroin also might predict increased use among adolescents who are more price sensitive in their use behaviors.

A University of Michigan online survey identified 13.9% misuse of opioids among nearly 3000 adolescents. Among misuse, a medical reason was most common and was associated with increased pain, anxiety, depression, and a history of sexual victimization. The other large grouping for misuse was nonmedical abuse that included predilection toward rule-breaking behavior, aggressive behavior, risk for substance dependence, and use of illicit drugs.

Of particular concern are findings of the potential for abuse even among appropriate uses of opioids because many current providers were taught that the risk of misuse among patients with appropriate indications was particularly low. Among a nationally representative sample of high school seniors, legitimate indication for and opioid use before graduation from high school increased risk of nonmedical use of a prescription opioid between the ages of 19 and 23 years by 33%. These patients had little or no history of drug use and appropriately negative views of illegal drug use at baseline. Further findings similar to these could certainly change the risk benefit equation for many pediatricians in regard to prescription of opioids.

Similarly, most providers would think that aberrant opioid-associated behaviors would be minimal in a population for which opioids are clearly indicated, such as cancer treatment. However, a study of an academic pediatric oncology practice identified a 11.7% rate of misuse. Examples of inappropriate behaviors included requesting specific drugs by brand names, resisting regimen changes, excessive phone calls to obtain more medication without a visit, and seeking pain treatment from multiple providers. Risk factors for substance abuse included history of prior addiction, anxiety, depression, attention-deficit/hyperactivity disorder, or some other mental health disorder.

In drug-naïve patients, the opioid prescription may represent their first interaction with an addictive drug. The initial experience is likely pleasurable and safe—a key factor in many theories of drug abuse. On the other hand, a legitimate prescription for an opioid is less likely to make a large impact on a patient with more exposure to other drugs. When one considers these factors in the face of the previous discussion about where children are getting opioids, the pediatrician may have great concern about general prescribing practices of opioids.

**Opioids as a gateway**
Alcohol, cigarettes, and marijuana are individually associated with current abuse of prescription opioids.

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Since 2007, drug overdoses have killed more people in Ohio than any other cause of accidental death, surpassing car accidents.

—Senator Rob Portman (R-Ohio), April 7, 2016, floor of the US Senate.

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1970
Oxycodone, along with all other opiates, is made a Schedule II drug under the federal Controlled Substances Act.

1973
The Drug Enforcement Agency is created by Executive Order.

1984
FDA approves Vicodin.
among 18- to 25-year-old men, but only marijuana use was similarly associated with young women in one study pooling data from the 2006, 2007, and 2008 National Survey on Drug Use and Health. Prescription opioid use also may be a gateway to heroin use despite a 10-fold greater prevalence of prescription opioid use. This is hypothesized to be attributed to rising costs for prescription opioids, a declining cost of heroin, and the increased potency of heroin providing a cheaper/better alternative, especially once addiction is established.

How to screen for opioid problems
Given the width and breadth of the opioid problem, multiple approaches are required. Because of the greater impact of opioids on younger patients, it is essential to limit the access of prescription opioids to children and adolescents who would abuse them while still providing adequate pain management to those who need it.

SCREENING
Substance abuse screening tools such as the CAGE-AID and CRAFFT are validated tools that can be used to briefly assess adolescents for substance use disorders. The tools can be used in the busy pediatric practice to identify if a more in-depth conversation about drug use is appropriate.

EDUCATION
The pediatrician must restrict opioid prescriptions to patients who truly need them. The pediatrician and clinical staff need to be educated about the risks of opioid misuse and also how to appropriately counsel parents about opioid risks. Furthermore, pediatricians need to discuss not only the risk of accidental ingestion because of the presence of opioids in a home, but also the risks related to nonmedical use of opioids among adolescents.

The future risk of the opioid-naïve patient should be considered in both prescribing decisions and patient counseling efforts given the emerging literature on the risk of short-term prescriptions with current and future misuse. Because of these risks, the pediatrician should consider discussing and offering nonopioid therapy for the treatment of minor painful conditions. One strategy might be to employ nonopioid therapy first line and reserve opioids for patients in whom these treatments are insufficient. Likewise, both parents and the pediatrician need to monitor for signs of misuse among patients for whom opioid treatments are appropriate.

Conclusions
Opioids are likely a growing problem for the pediatric practice whether or not the pediatrician recognizes the problem in his or her community. The misconception that opioid problems are centered among lower socioeconomic parts of society may be preventing pediatricians from more fully addressing this problem in their practices. Emerging evidence indicates that very small exposures of opioids can lead to future problems for the pediatric patient. As a result, all pediatricians may need to carefully examine their own prescribing practices.
Midazolam warning for preemies

Midazolam has been associated with disruption in hippocampal development in preterm infants.

ILYA PETROU, MD
A recent study in preterm infants found that exposure to midazolam, a commonly used sedative in the neonatal intensive care unit (NICU), was associated with macro- and microstructural alterations in hippocampal development and poorer outcomes consistent with hippocampal dysmaturatation. With the optimal care of the individual patient in mind, clinicians could potentially use alternative sedative and narcotic medications that are available to help circumvent the adverse events associated with midazolam.

On average, very preterm infants (24 to 32 weeks of gestation) will spend approximately 3 months in the NICU, and in that time will undergo approximately 12 invasive procedures every day. Benzodiazepines such as midazolam are commonly used in the NICU to help minimize the pain and stress associated with the many clinical procedures that these preterm infants need to undergo during their several months-long stay in intensive care.

"Preterm babies often have to undergo hundreds of painful and uncomfortable procedures during the NICU stay. As shown by our group and others, pain is bad for babies and some commonly used analgesics and sedatives may also have adverse effects on brain development," says Emma Gail Duerden, PhD, senior research associate, Neonatal Imaging Program, the Hospital for Sick Children (SickKids) and University of Toronto, Ontario, Canada.

Duerden and colleagues recently conducted a study to assess the effect of invasive procedures and analgesic-sedative exposure on hippocampal growth, as well as hippocampal growth on neurodevelopmental outcome.1 The study included 138 neonates (51% male; median gestational age, 27.7 weeks) who underwent magnetic resonance imaging and diffusion tensor imaging (DTI) scans early in life (postmenstrual age [PMA], 32.3 weeks) and at term-equivalent age (PMA, 40.2 weeks). Volumes and DTI measures of axial diffusivity, radial diffusivity, and mean diffusivity were obtained from the hippocampus. Cognitive, language, and motor abilities were assessed using the Bayley Scales of Infant Development-III at 18.7 months median correlated age. Models testing the association of invasive procedures with hippocampal volumes and DTI measures accounted for birth gestational age, sex, PMA, dose of analgesics/sedatives (fentanyl, morphine, midazolam), mechanical ventilation, hypotension, and surgeries.

Data showed that midazolam exposure predicted slower development of the hippocampus, a key brain structure for memory, as preterm neonates grew to term-equivalent age. In addition, it was found that poorer cognitive development at 18 months was associated with slower hippocampal growth and midazolam exposure. Given these findings, Duerden says that the use of midazolam in very preterm neonates is cautioned, as more research is needed in the area.

It is important to note that although (midazolam and other) benzodiazepines provide sedation, they have no analgesic effect.

Treatment of opioid use disorder

New guidelines can arm pediatricians with the basic understanding of treatment options to manage opioid dependence or addiction in children.

MARY BETH NIERENGARTEN, MA

As problems with opioid use and abuse in the United States increasingly emerge to create what is being called a public health epidemic, clinicians are facing the great challenge of trying to provide optimal pain management for their patients while being mindful of the potential deleterious effects of the highly addictive opioids. When used properly, these drugs provide great pain relief, but their easy misuse and abuse create a cascade of problems that has led to current debates on their appropriate and best use for pain management.

Within this larger debate is the difficult issue of how to treat patients who become dependent or addicted to opioids. For pediatricians and other healthcare providers who care for children who develop an opioid dependence or addiction, the challenge to treat this dependence is all the greater given the lack of good guidelines geared particularly for children and adolescents.

Conflicting guidelines for kids

The need for guidance is critical. Prescription of opioids to US children for medical reasons has doubled over the past decade, with the majority of opioids prescribed for postprocedural and postoperative use in children aged between 10 and 17 years of age. New guidelines can arm pediatricians with the basic understanding of treatment options to manage opioid dependence or addiction in children..Methodology

New guidelines can arm pediatricians with the basic understanding of treatment options to manage opioid dependence or addiction in children.

MARY BETH NIERENGARTEN, MA

The need for guidance is critical. Prescription of opioids to US children for medical reasons has doubled over the past decade, with the majority of opioids prescribed for postprocedural and postoperative use in children aged between 10 and 17 years of age. New guidelines can arm pediatricians with the basic understanding of treatment options to manage opioid dependence or addiction in children.
### American Society of Addiction Medicine National Practice Guideline: Assessment and Diagnosis

<table>
<thead>
<tr>
<th>Table 1</th>
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</thead>
<tbody>
<tr>
<td><strong>Assessment</strong></td>
</tr>
<tr>
<td>○ Identify and refer any urgent or emergent medical or psychiatric problems (including drug-related or overdose).</td>
</tr>
<tr>
<td>○ Conduct a comprehensive assessment that includes medical history (screen for concomitant medical conditions such as hepatitis, HIV, TB); physical exam; relevant lab tests; mental health status; evaluation of past and current substance abuse; social and environmental factors.</td>
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</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>○ Diagnosis is made primarily by patient history and comprehensive assessment.</td>
</tr>
<tr>
<td>○ Clinicians can diagnose opioid use disorder but a diagnosis must be confirmed by the provider with prescribing authority before pharmacotherapy for opioid use disorder can begin.</td>
</tr>
<tr>
<td>○ Withdrawal symptoms can be measured by using various validated clinical scales.</td>
</tr>
<tr>
<td>○ Urine drug testing during assessment and during treatment is recommended.</td>
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</tbody>
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Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.
From Kampman K, et al.1

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In 2009, more than 7 million prescriptions for opioids were dispensed for children. Accompanying this increase in opioid prescriptions are the numbers that tell the problem. According to data from the Centers for Disease Control and Prevention (CDC), nearly 2 million people in the United States aged 12 years and older either abused or became dependent on opioids in 2013.2 In addition, 2.6 of 100,000 persons in the United States aged between 15 and 24 years died from an overdose of prescription opioids.

The recently published 2016 guideline from the CDC on prescribing opioids for chronic pain, which includes a recommendation for evidence-based treatment for opioid use disorder, provides needed guidance for adults, and it explicitly states that the guidelines apply only to patients aged 18 years or older.3 However, as emphasized in an accompanying editorial, pediatricians and primary care providers should take care not to extrapolate from this evidence geared toward adults and tailor it inappropriately, and perhaps with detriment, to children and adolescents.2

In 2014, the American Academy of Pediatrics (AAP) published a clinical report on management strategies for weaning children and adolescents off opioids (at the same time emphasizing the lack of clear evidence on a single ideal protocol). Highlighted is the need for gradual dose reduction without abrupt drug discontinuation.1 Although no management strategies were provided for how to treat children and adolescents who become dependent on or addicted to opioids, the clinical report does reference data from treatment programs for adolescents who are dependent on prescription opioids or heroin that include behavioral intervention in their treatment programs (For the description of an attempt by a US tertiary care children’s hospital to standardize management of iatrogenically induced opioid dependence and withdrawal—“Treatment of opioid dependence: Protocol developed at a tertiary care children’s hospital”—go to ContemporaryPediatrics.com/opioid-treatment.4)

Although no singular guideline exists that specifically focuses on treatment of opioid dependence or addiction in children and...
### ASAM NATIONAL PRACTICE GUIDELINE: TREATMENT

**Treatment options**
- Choice of treatment should be based on shared decision between clinician and patient.
- Venue for treatment is important as is the specific medication selected (see below on individual drugs).

**Treating opioid withdrawal**
- Using medications for opioid withdrawal is recommended over abrupt discontinuation.
- See guidelines for specific recommendations.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Details</th>
</tr>
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<tbody>
<tr>
<td><strong>Methadone</strong></td>
<td>Recommended for patients who are physiologically dependent on opioids and with no specific contraindications for agonist treatment. Recommended initial dose ranges from 10-30 mg; reassess in 3-4 h and for persistent symptoms a second dose can be given that does not exceed 10 mg (first d). Usual daily dose ranges from 60-120 mg, but dosing depends on patient response that can vary. Dose increases in 5-10 mg increments can be applied, but not more frequently than every 7 d depending on clinical response. Monitor treatment. Switching to another medication may be appropriate in cases of intolerant adverse effects or insufficient response. If switching to buprenorphine, patient should first be on low doses of methadone (30-40 mg/d or less). If switching to naltrexone, patient should be completely withdrawn from methadone and other opioids.</td>
</tr>
<tr>
<td><strong>Buprenorphine</strong></td>
<td>First dose should be given only when patient is experiencing mild-to-moderate opioid withdrawal to reduce risk of precipitated withdrawal. Induction starts with a dose of 2-4 mg; clinicians should observe patients in their offices during induction. Doses may be increased by increments of 2-4 mg. Once initial dose is well tolerated, the dose can be increased fairly rapidly to a dose providing stable effects for 24 h. Patients should be seen frequently at the beginning of treatment; weekly visits are recommended. Buprenorphine tapering is slow and takes months, and requires close monitoring even after discontinuation. If switching to methadone, no time delay in switching is required.</td>
</tr>
<tr>
<td><strong>Naltrexone</strong></td>
<td>Recommended for preventing relapse. Oral formula should be taken daily in 50 mg doses, or 3 times wk in 2, 100-mg doses followed by 1, 150-mg dose. Extended-release injectable formula should be administered every 4 wk by deep intramuscular injection in the gluteal muscle at a set dosage of 380 mg/injection. No recommended length of treatment. Switching to methadone or buprenorphine requires planning and monitoring; do not switch until a significant amount of naltrexone is no longer in the patient’s system (about 1 d for oral naltrexone or 30 d for injectable naltrexone).</td>
</tr>
<tr>
<td><strong>Psychosocial treatment in conjunction with drug treatment</strong></td>
<td>Psychosocial treatment is recommended in conjunction with pharmacologic treatment, including assessment of psychosocial needs, supportive counseling, links to family supports, and referrals to community services. Treatment planning should be done in collaboration with a qualified behavioral healthcare provider.</td>
</tr>
</tbody>
</table>

**Abbreviation:** ASAM, American Society of Addiction Medicine.

From Kampman K, et al.5

Maker of OxyContin agrees to pay about $600 million when it pleads guilty to federal criminal charges for marketing OxyContin as a drug that was less addictive, less subject to abuse, and less likely to cause other narcotic adverse effects than other pain medications.
Introducing a flu shot that could help transform flu protection

For decades, there have been few new developments in flu shot manufacturing.1 Now, there’s a vaccine made using a modern process that could help transform flu protection for your patients. FLUCELVAX QUADRIVALENT is made using cell culture technology, which does not require eggs for manufacturing and has the potential for rapidly increased production of flu shots in times of need.1,2 It’s also antibiotic, preservative, and latex free, and it helps protect against 4 strains of the flu in people aged 4 years and older.2

In clinical studies, FLUCELVAX QUADRIVALENT was immunogenic against the flu, and in adults, it produced stronger antibody responses to the B strain, which was not contained in the trivalent comparator flu vaccine.3 FLUCELVAX QUADRIVALENT was also shown to be well tolerated.2 This flu season, consider a flu shot that’s on the cutting edge of flu protection. Choose FLUCELVAX QUADRIVALENT.


Indication and Usage for FLUCELVAX QUADRIVALENT® (Influenza Vaccine)

FLUCELVAX QUADRIVALENT® is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUCELVAX QUADRIVALENT is approved for use in persons 4 years of age and older.

IMPORTANT SAFETY INFORMATION

Contraindications:
• Do not administer FLUCELVAX QUADRIVALENT to anyone with a history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine.

Warnings & Precautions:
• Guillain-Barré Syndrome (GBS): If GBS has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLUCELVAX QUADRIVALENT should be based on careful consideration of the potential benefits and risks.
• Preventing and Managing Allergic Reactions: Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.
• Syncope: Syncope (fainting) can occur in association with administration of injectable vaccines, including FLUCELVAX QUADRIVALENT. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope by maintaining a supine or Trendelenburg position.
• Altered Immunocompetence: After vaccination with FLUCELVAX QUADRIVALENT, immunocompromised individuals, including those receiving immunosuppressive therapy, may have a reduced immune response.

• Limitations of Vaccine Effectiveness: Vaccination with FLUCELVAX QUADRIVALENT may not protect all vaccine recipients against influenza disease.

Most Common Adverse Reactions:
• The most common (≥10%) local and systemic reactions in adults 18-64 years of age were injection site pain (45.4%), headache (18.7%), fatigue (17.8%) and myalgia (15.4%), injection site erythema (13.4%), and induration (11.6%).
• The most common (≥10%) local and systemic reactions in adults ≥65 years of age were injection site pain (21.6%) and injection site erythema (11.9%).
• The most common (≥10%) local and systemic reactions in children 4 to <6 years of age at the injection site (46%), injection site erythema (18%), sleepiness (16%), irritability (16%), injection site induration (15%), and change in eating habits (10%).
• The most common (≥10%) local and systemic reactions in children 6 through 8 years of age were pain at the injection site (54%), injection site erythema (22%), injection site induration (16%), headache (14%), fatigue (13%), and myalgia (12%).
• The most common (≥10%) local and systemic reactions in children and adolescents 9 through 17 years of age were pain at the injection site (58%), headache (22%), injection site erythema (19%), fatigue (18%) myalgia (16%), and injection site induration (15%).

Please see Brief Summary of Prescribing Information for FLUCELVAX QUADRIVALENT adjacent to this ad.

BRIEF SUMMARY: See package insert for full Prescribing Information.

1 INDICATIONS AND USAGE
FLUCELVAX QUADRIVALENT® is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUCELVAX QUADRIVALENT is approved for use in persons 4 years of age and older. For children and adolescents 4 through 17 years of age, approval is based on the immune response elicited by FLUCELVAX QUADRIVALENT. Data demonstrating a decrease in influenza disease after vaccination of this age group with FLUCELVAX QUADRIVALENT are not available. [see Clinical Studies (14)]

4 CONTRAINDICATIONS
Do not administer FLUCELVAX QUADRIVALENT to anyone with a history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine.

4.1 Guillain-Barré Syndrome
The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated. If GBS has occurred after receipt of a prior influenza vaccine, the decision to give FLUCELVAX QUADRIVALENT should be based on careful consideration of the potential benefits and risks.

5.1 Guillain-Barré Syndrome
The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated. If GBS has occurred after receipt of a prior influenza vaccine, the decision to give FLUCELVAX QUADRIVALENT should be based on careful consideration of the potential benefits and risks.

5.2 Preventing and Managing Allergic Reactions
Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

5.3 Syncope
Syncope (fainting) can occur in association with administration of injectable vaccines, including Flucelvax. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope by maintaining a supine or Trendelenburg position.

5.4 Altered Immunocompetence
After vaccination with FLUCELVAX QUADRIVALENT, immunocompromised individuals, including those receiving immunosuppressive therapy, may have a reduced immune response.

5.5 Limitations of Vaccine Effectiveness
Vaccination with FLUCELVAX QUADRIVALENT may not protect all vaccine recipients against influenza disease.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
The most common (≥10%) local and systemic reactions in adults 18-64 years of age were injection site pain (45.4%), headache (18.7%), fatigue (17.8%), and myalgia (15.4%). Injection site erythema (13.4%), and induration (11.6%).

6.2 Solicited Reactions
The safety population included a total of 2332 children 4 through 17 years of age. A total of 1335 children (N=1335), TIV1c, N=676 or TIV2c N=669. The mean age of subjects who received FLUCELVAX QUADRIVALENT was 57.4 years of age; 54.8% of subjects were female and 75.6% were Caucasian, 13.4% were Black, 9.1% were Hispanics, 0.7% were American Indian and 0.3%, 0.1% and 0.7% were Asian, Native Hawaiian and others, respectively. The safety data observed are summarized in Table 2.

In this study, solicited local injection site and systemic adverse reactions were collected from subjects who completed a symptom diary card for 7 days following vaccination.

Solicited adverse reactions for FLUCELVAX QUADRIVALENT and comparator are summarized in Table 2.

6.3 Unsolicited Reactions
Unsolicited adverse reactions were collected from subjects who completed a symptom diary card for 7 days following vaccination.

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

6.5 Vaccine Effectiveness
FLUCELVAX QUADRIVALENT is approved for use in persons 4 years of age and older.

6.6 Laboratory Tests
FLUCELVAX QUADRIVALENT contains no preservatives, thimerosal, or other substances that have been associated with adverse reactions in clinical use of influenza vaccines. [see Clinical Studies (14)]

6.7 Experience in Specified Special Populations
FLUCELVAX QUADRIVALENT is not recommended for use in immunocompromised individuals, including those receiving immunosuppressive therapy, who may have a reduced immune response.

6.8 Pregnancy
It is not known whether FLUCELVAX QUADRIVALENT can cause fetal harm when administered to a pregnant woman. The use of vaccines during pregnancy has generally not been associated with adverse effects on the fetus or with problems at parturition. A small number of US commercial vaccines have been shown to be associated with increased risk of idiopathic thrombocytopenic purpura in the first trimester. FLUCELVAX QUADRIVALENT is not recommended for use in immunocompromised individuals, including those receiving immunosuppressive therapy, who may have a reduced immune response.

6.9 Immunocompromised Populations
FLUCELVAX QUADRIVALENT is not recommended for use in immunocompromised individuals, including those receiving immunosuppressive therapy, who may have a reduced immune response.

6.10 Pregnancy
It is not known whether FLUCELVAX QUADRIVALENT can cause fetal harm when administered to a pregnant woman. The use of vaccines during pregnancy has generally not been associated with adverse effects on the fetus or with problems at parturition. A small number of US commercial vaccines have been shown to be associated with increased risk of idiopathic thrombocytopenic purpura in the first trimester. FLUCELVAX QUADRIVALENT is not recommended for use in immunocompromised individuals, including those receiving immunosuppressive therapy, who may have a reduced immune response.

6.11 Pediatric Use
FLUCELVAX QUADRIVALENT is recommended for use in children 6 months of age and older, including children with chronic medical conditions.
In this study, subjects received FLUCELVAX QUADRIVALENT or one of the two formulations of comparator trivalent influenza vaccine (FLUCELVAX QUADRIVALENT (N=1159), TIV1c, N=593 or TIV2c N= 580). Children 9 through 17 years of age received a single dose of FLUCELVAX QUADRIVALENT or comparator vaccine. Children 4 through 8 years of age received one or two doses (separated by 4 weeks) of FLUCELVAX QUADRIVALENT or comparator vaccine based on determination of the subject’s prior influenza vaccination history. The mean age of subjects who received FLUCELVAX QUADRIVALENT was 9.6 years of age; 48% of subjects were female and 53% were Caucasian. The safety data observed in this study are summarized in Table 3 and Table 4.

Table 3: Incidence of Solicited Adverse Reactions in the Safety Population1 (4 through 5 years of age) Reported Within 7 Days of the First Dose of Vaccination (Study 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>FLUCELVAX QUADRIVALENT (N=1132)</th>
<th>Trivalent Influenza Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TIV1c N=591</td>
<td>TIV2c N=551</td>
</tr>
<tr>
<td>Injection site induration</td>
<td>14 (1)</td>
<td>20 (2)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>18 (1)</td>
<td>23 (1)</td>
</tr>
<tr>
<td>Injection site ecchymosis</td>
<td>9 (0)</td>
<td>11 (0)</td>
</tr>
<tr>
<td>Injection site tenderness</td>
<td>48 (1)</td>
<td>45 (1)</td>
</tr>
</tbody>
</table>

Table 4: Incidence of Solicited Adverse Reactions in the Safety Population2 (4 through 5 years of age) Reported Within 7 Days of the First Dose of Vaccination (Study 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>FLUCELVAX QUADRIVALENT (N=371-372)</th>
<th>Trivalent Influenza Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TIV1c N=185</td>
<td>TIV2c N=186</td>
</tr>
<tr>
<td>Injection site induration</td>
<td>16 (0)</td>
<td>19 (1)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>22 (0)</td>
<td>23 (1)</td>
</tr>
<tr>
<td>Injection site ecchymosis</td>
<td>9 (0)</td>
<td>9 (0)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>54 (1)</td>
<td>57 (1)</td>
</tr>
</tbody>
</table>

1 Safety population: all subjects in the exposed population who provided post-vaccination safety data.
2 Percentage of subjects with severe adverse reactions are presented in parenthesis. Study 2: NCT 01992107

In children who received a second dose of FLUCELVAX QUADRIVALENT, TIV1c, or TIV2c, the incidence of adverse reactions following the second dose of vaccine were similar to those observed with the first dose.

Unsolicited adverse events, including serious adverse events, were collected for 21 days after last vaccination. In children 4 through 17 years of age, unsolicited adverse events were reported in 24.3% of subjects who received FLUCELVAX QUADRIVALENT within 3 weeks after last vaccination.

In children 4 through 17 years of age, serious adverse events (SAEs) were collected throughout the study duration (until 6 months after last vaccination) and were reported by 0.5%, of the subjects who received FLUCELVAX QUADRIVALENT. None of the SAEs were assessed as being related to study vaccine.

### 6.2 Postmarketing Experience

The safety experience with FLUCELVAX (trivalent influenza vaccine) is relevant to FLUCELVAX QUADRIVALENT, because both vaccines are manufactured using the same process and have overlapping compositions.

The following additional adverse events have been identified during post-approval use of FLUCELVAX. Because these events 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.

**Immune system disorders:** Anaphylactic reaction, angioedema.

**Skin and subcutaneous tissue disorders:** Generalized skin reactions including pruritus, urticaria or non-specific rash.

**Nervous system disorders:** Syncope, Presyncope

**General disorders and administration site conditions:** Extensive swelling of injected limb.

### 7 DRUG INTERACTIONS

#### 7.1 Concomitant Use With Other Vaccines

No data are available to assess the concomitant administration of FLUCELVAX QUADRIVALENT with other vaccines.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

Pregnancy Category B: The developmental and reproductive toxicity study performed with the trivalent formulation of Flucelvax is relevant to Flucelvax Quadrivalent because both vaccines share the same manufacturing process and route of administration. A reproductive and developmental toxicity study has been performed in rabbits with Flucelvax, with a dose level that was approximately 11 times the human dose based on body weight. The study revealed no evidence of impaired female fertility or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this vaccine should be used during pregnancy only if clearly needed.

In a reproductive and developmental toxicity study, the effect of Flucelvax containing 45 mcg HA/dose on embryo-fetal and post-natal development was evaluated in pregnant rabbits. Animals were administered vaccine by intramuscular injection 3 times prior to gestation, during the period of organogenesis (gestation day 7) and later in pregnancy (gestation day 20), 0.5 mL/rabbit/occasion (approximately 11-fold excess relative to the projected human dose on a body weight basis). No adverse effects...
adolescents, a recently published guideline by the American Society of Addiction Medicine (ASAM) on the use of medications to treat addiction involving opioid use includes a specific section on treatment for adolescents.5

This article summarizes key treatment strategies from the ASAM guideline. Its aim is not to provide a single approach or guideline on how to treat opioid dependence or addiction in children (as none yet exists), but to arm pediatricians with some basic understanding of treatment considerations as they either refer their patients to or collaborate with addiction specialists to provide the best treatment possible for their patients.

8.3 Nursing Mothers
FLUCELVAX QUADRIVALENT has not been evaluated in nursing mothers. It is not known whether FLUCELVAX QUADRIVALENT is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLUCELVAX QUADRIVALENT is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness have not been established in children less than 4 years of age.

8.5 Geriatric Use
Of the total number of subjects who received one dose of FLUCELVAX QUADRIVALENT in clinical studies and included in the safety population (2493), 26.47% (660) were 65 years of age and older and 7.7% (194) were 75 years of age or older.

Antibody responses to FLUCELVAX QUADRIVALENT were lower in the geriatric (adults 65 years and older) population than in younger subjects. [see Clinical Studies (14.3)]

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clinical feature

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DISTINCTION BETWEEN OPIOID DEPENDENCE AND ADDICTION

Physical adaptation to an opioid manifested by withdrawal syndrome produced by abrupt cessation of the drug, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

From Galinkin J, et al.1

Primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors that influence its development, and is characterized by such behaviors as impaired control over opioid use, compulsive use, continued use despite harm, and craving.

ASAM treatment guidelines
Published in 2015, the ASAM practice guideline focuses on the use of medications to treat addiction involving opioid use and provides a number of clinical recommendations based on 13 different areas (or parts).5 These areas include assessment and diagnosis; treatment options; treating
opioid withdrawal; methadone; buprenorphine; naltrexone; psychosocial treatment in conjunction with medications for the treatment of opioid use disorder; special populations (pregnant women, individuals with pain, adolescents, individuals with co-occurring psychiatric disorders, individuals in the criminal justice system); and naloxone for the treatment of opioid overdose.

This article only summarizes those areas most relevant to pediatricians and other healthcare providers in treating opioid dependence or addiction in children and adolescents. Tables 1 and 2 summarize clinical recommendations that pertain to all populations with opioid dependence, and can be relevant for (but are not specific to) children and adolescents. These tables provide only a brief summary, therefore readers are urged to read the full clinical guideline. Table 3 summarizes recommendations specific for adolescents.

**Summary**

To date, no singular guideline exists on treatment of opioid dependence or addiction in children and adolescents. Current guidelines on opioid use and treatment are geared primarily for adults, and their extrapolation to children should be avoided because little data is available on the specific effects of opioids on the developing mind and the optimal approach to treating dependence or addiction. Pediatricians and other healthcare providers who care for children and adolescents can use the information here as a starting point to better understand how to approach the management of opioid dependence or addiction in children.

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**For references, go to ContemporaryPediatrics.com**

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**ASAM NATIONAL PRACTICE GUIDELINE: CONSIDERATIONS SPECIFIC TO CHILDREN AND ADOLESCENTS**

| Consider all treatment options | • Pharmacotherapy, including opioid agonists (methadone and buprenorphine) and antagonists (naltrexone)  
| Recognize and consider federal laws and FDA approvals when using drug therapy for patients aged younger than 18 y | • Buprenorphine: FDA-approved for patients aged 16 y and older.  
| | • Methadone: No data from clinical trials in patients aged younger than 18 y. Federal code on opioid treatment offers an exception for patients aged 16 y and 17 y with a documented history of at least 2 prior unsuccessful withdrawal management attempts, and who have parental consent.  
| | • Naltrexone: May be considered for treatment for patients aged 18 y and older.  
| Consider concurrent practices to prevent and reduce infection from STDs | • Provide concurrent practices, such as sexual risk reduction intervention, to reduce and prevent infection from STDs and blood-borne viruses.  
| Understand importance of confidentiality | • Particularly important when treating adolescents, who report they are less likely to seek treatment if discussion is not kept confidential.  
| | • Clinicians need to understand the clinical and legal responsibilities when adolescents ask for confidentiality.  
| | • By law, adolescents aged younger than 18 y are permitted to consent to addiction treatment without parental consent in over half the states in the United States.  
| Consider specialized treatment facilities | • Adolescents may benefit from receiving treatment in a specialized treatment facility that provides multidimensional services.  

Abbreviations: ASAM, American Society of Addiction Medicine; FDA, US Food and Drug Administration; STD, sexually transmitted disease.

From Kampman K, et al.5
Chest wall rigidity in fentanyl abuse

Illegally sourced fentanyl is often taken intravenously, which can lead to chest wall rigidity, a potentially lethal adverse event. Henry A. Spiller, MS, DABAT, FAACFT, Director of the Central Ohio Poison Center at Nationwide Children’s Hospital, has noted an increase in fentanyl-related deaths, which he attributes to rapid intravenous administration.

A recent study confirmed that chest wall rigidity is a contributing factor in fatalities caused by intravenous injection of fentanyl. Using liquid chromatography tandem mass spectrometry, researchers were able to quantify fentanyl, norfentanyl, alfentanyl, and sulfentanyl. The concentrations of fentanyl ranged from 0.5 ng/ml to >40 ng/ml, and the mean norfentanyl concentrations were 1.9 ng/ml (range: none detected to 8.3 ng/ml). No appreciable concentrations of norfentanyl could be detected in 20 of 48 cases (42%), and concentrations were less than 1 ng/ml in 25 cases (52%). In several cases, fentanyl concentrations were significantly high (22 ng/ml and 20 ng/ml) without any detection of norfentanyl.

“We believe these results are highly suggestive of fentanyl playing a role in chest wall rigidity. Not all of the deaths were suspect of chest wall rigidity, as there were detectable metabolites in several cases. However, approximately half of our cases did not have any measurable level of norfentanyl, which suggests a very rapid death consistent with chest wall rigidity,” Spiller says.

Although drug intoxication can occur with any of the opiates, fentanyl is a very potent one.
In the throes of an opioid epidemic, the US Food and Drug Administration (FDA) decided in August 2015 to expand the indications for OxyContin, an extended-release form of the narcotic oxycodone, to children aged 11 years and older.

The decision sparked outrage in those who fear the move might fuel increasing opioid addiction among young Americans. Those for the change say it will give prescribers more information about how best to use the drug in children and could lead to better prescribing patterns.

Both sides agree, however, that responsible prescribing and patient compliance are at the heart of using the drug optimally in children who need it most.

The FDA’s intention, according to Janet Woodcock, MD, director of the FDA’s Center for Drug Evaluation and Research, is to provide safety and dosing information to physicians caring for a very small group of seriously ill and vulnerable children.

“[I]t is limited to opioid-tolerant pediatric patients 11 and up who are already taking and tolerating a minimum daily dose of at least 20 mg oxycodone orally or its equivalent and are in pain severe enough to require daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate,” Woodcock wrote in an e-mail.
The safety of OxyContin in pediatric patients has been evaluated in an open-label clinical trial of 155 opioid-tolerant pediatric patients aged 6 to 16 years with moderate to severe chronic pain. Use is limited to children aged 11 years and older because there were only 15 patients aged younger than 11 years who were studied. The mean duration of therapy was 20.7 days (range, 1 to 43 days). The mean daily dose was 33.30 mg, with a range of 20 mg to 140 mg daily. In an extension study, 23 of the 155 patients were treated beyond 4 weeks; 13 of those were treated for 28 weeks, according to Woodcock.

**Pro labeling change**

Kathleen A. Neville, MD, MS, MBA, pediatric oncologist and chief of the section of clinical pharmacology and toxicology at Arkansas Children’s Hospital, Little Rock, and chairwoman of the Committee on Drugs at the American Academy of Pediatrics, says she thinks this is a move in the direction of better prescribing practices. The FDA has postmarketing requirements of OxyContin’s manufacturer Purdue Pharma (Stanford, Connecticut) that will help to track prescriptions to children and arm providers with important prescribing information.

“I actually think [the results of the clinical trial] may lead to less prescribing,” Neville says. “Before, there was a lack of knowledge and people would prescribe what they think and use it off label. But now there are clear guidelines about who the appropriate patient population is. And the company is required to do surveillance.”

**The New York Times** reported in October last year that the FDA is requiring Purdue Pharma to conduct postapproval studies, including 1 study with adverse event annual reporting and a comprehensive analysis of respiratory depression, overdoses, and more. Purdue is also required to report nationally representative data on the volume of OxyContin prescriptions for children aged younger than 17 years, and the clinician types prescribing OxyContin and for what conditions.1

Any information that can be gathered and used to better prescribe opioids in children is an improvement, according to Neville. There’s no labeling information for children for morphine or methadone, and there’s scant information on other narcotics. “When prescribing any narcotic, there’s less information on children than adults,” she says. “That’s why I view this as an accomplishment.”

Sharon Levy, MD, MPH, director, Adolescent Substance Abuse Program, Boston Children’s Hospital, and associate professor of pediatrics at Harvard Medical School, Boston, Massachusetts, says she understands the concern that the new labeling could lead to more prescribing in the age group, but thinks it’s unlikely to happen in an environment in which physicians are getting more and more education about the risks of opioid use.

“Like adults, children can have extremely painful experiences—for example injuries and surgical procedures—and it is very important that they have access to appropriate pain medications,” Levy wrote in an e-mail...
Appropriate diagnosis of respiratory symptoms is critical to patient management and antimicrobial stewardship, especially with children. Several studies have documented that physicians feel pressured by parents to prescribe antimicrobials for respiratory infections. Overprescribing of antibiotics for viral illness is a factor contributing to increasing antimicrobial resistance among bacterial pathogens encountered in pediatrics.¹

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to Contemporary Pediatrics. Having a formal indication allows these medications to be included in formal guidelines, which helps physicians make treatment decisions, she notes.

Is this a bad move?
The FDA made a terrible mistake, according to Andrew Kolodny, MD, senior scientist at the Heller School for Social Policy and Management at Brandeis University, Waltham, Massachusetts; executive director for Physicians for Responsible Opioid Prescribing (PROP); and chief medical officer for Phoenix House, a national nonprofit addiction agency. “I think it was an awful decision on several levels. I don’t even know where to begin,” he says.

In 2013, PROP filed a petition with the FDA to narrow the indication on opioid labels for the then-adult indication because of the concern that OxyContin was being promoted for chronic noncancer pain, a condition for which opioids haven’t been proven safe and effective, according to Kolodny.2

“When that label change effort was made, FDA agreed that evidence was lacking to support opioids as safe and effective for long-term use and at that point required manufacturers to start doing long-term studies to demonstrate whether or not opioids are safe and effective for chronic noncancer pain,” he says. “Those studies never came in. So even though FDA agrees that opioids may not be safe and effective for adults with chronic pain, it allowed a new label indication for use in children with chronic pain.”

Studies supporting long-term use of OxyContin for chronic pain are still lacking, and increasing evidence suggests that risks of chronic use may outweigh benefits, Kolodny says. The director of the Centers for Disease Control and Prevention (CDC), Thomas R. Frieden, MD, MPH, recently wrote in a New England Journal of Medicine editorial that whereas “the benefits of opioids for chronic pain remain uncertain, the risks of addiction and overdose are clear.”3

Kolodny says another concern is that although Purdue Pharma has indicated it will not promote OxyContin for use in children and, hopefully, the company will keep its word, we shouldn’t be at the mercy of a drug company trying to do the right thing. Purdue Pharma was punished with some $600 million in fines in 2007 for misleading OxyContin marketing practices. (See “Oxy’s checkered marketing history” online at ContemporaryPediatrics.com/OxyContin-labeling.)

Drug studies are needed in children, says Kolodny, and he thinks it’s worthwhile for the FDA to try to incentivize drug companies to research use of medications for children. However, he also believes that studying opioids in children with chronic pain raises ethical concerns. He criticized the FDA for failing to consider the increased risk of addiction in its decision to approve marketing of OxyContin for children.

“Before the brain is fully mature, we have reason to believe that addiction can set in more easily and become more lifelong and difficult to treat. We know this from studies on tobacco, that the younger somebody starts smoking the more likely [he/she is] to become a lifelong smoker and the more difficult it is to treat [his/her] nicotine addiction,” Kolodny says. “That [higher addiction risk potential] was not considered or taken into account [in this decision].”

94,000

NUMBER OF PEOPLE WHO HAVE DIED SINCE 1999 FROM OVERDOSES INVOLVING OPIOID PAINKILLERS.

Nine US Senators write letter to Chair and Ranking Member of Senate Health, Education, Labor, and Pensions Committee calling for FDA to hold public hearings on its approval decision and the opioid epidemic in general. Letter cites the quadrupling of opioid prescriptions written annually since 1999.
Finally, Kolodny says the FDA didn’t heed its own policy on when to bring decisions before an advisory committee. The FDA, he explains, has 3 criteria to help it decide when to bring a decision to outside experts, and if any 1 of the 3 criteria is met, the FDA should consult outside experts. The criteria include if a decision is of significant public interest, if it would be potentially controversial, and if the FDA would benefit from consulting experts in certain disciplines. In Kolodny’s view, all 3 criteria were met and the FDA shouldn’t have approved the label extension without consulting an advisory committee.

“The argument FDA made is that by doing this we learn more about proper dosing in children, so that we can give better dosing guidance. That never happened. There is no difference in dosing on the pediatric label from the adult more cautious dosing.”

The bottom line is that Kolodny thinks the labeling change will increase the likelihood that more young people will become addicted.

There are certainly important reasons to prescribe opioids for end-of-life care and for acute pain, Kolodny says. “In those cases where an opioid is prescribed for an injury or for postoperative pain, [patients] should be exposed to the opioid at the lowest possible dose, for the shortest possible duration,” he says. “But this is an extended-release opioid, so you’re not giving it to the child when [his/her] pain becomes severe, and then stopping it as soon as the child is able to tolerate the pain. You’re putting [these children] on a dose that gives them round-the-clock opioid effects, and, if you do that, within just a few days, you’ve made the child physiologically dependent on the drug. And if you have the child on the drug for 30 days, there are neurologic changes that are visible on imaging studies. With OxyContin being one of the only opioids with a pediatric indication, I’m afraid some docs may prescribe it in place of a lower-dose immediate-release opioid. And that’s a really bad idea if the goal is to expose [the child] to as little opioid as possible.”

G. Caleb Alexander, MD, MS, a practicing internist and codirector of the Center for Drug Safety and Effectiveness at Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, says there are concerning inconsistencies with the FDA’s move to add pediatric indications to OxyContin’s labeling, and he thinks it could result in more prescribing of the drug to children. Before the label extension, pediatricians were free to prescribe OxyContin off label, in accordance with best practices, so the FDA approval was not required to permit such use, according to Alexander.

“The concern that has been raised by some is: Are we really at a point where we need more noninnovative opioids being approved? And I think many would argue no,” he says.

The suggestion that this move will encourage more research on OxyContin in children also is suspect, according to Alexander. The regulatory approval doesn’t necessarily encourage research, he says, but the FDA does incentivize manufacturers to study products on children by, in some cases, offering extra patent protection for those products.

“If Purdue is getting additional patent exclusivity for this label extension, all the more reason to have concern because essentially it

In 2011, hydrocodone was the fourth most commonly abused substance by Americans 14 years of age and older.

—2011, National Institute on Drug Abuse, NIH.
RotaTeq is indicated for the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, and G4 when administered as a 3-dose series to infants between the ages of 6 to 32 weeks.

The vaccination series consists of 3 ready-to-use liquid doses of RotaTeq administered orally starting at 6 to 12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals. The third dose should not be given after 32 weeks of age.

Selected Safety Information

RotaTeq should not be administered to infants with a demonstrated history of hypersensitivity to the vaccine or any component of the vaccine.

In the Rotavirus Efficacy and Safety Trial (REST)

**RotaTeq showed high-level efficacy against RGE caused by common serotypes G1, G2, G3, and G4 through the first rotavirus season postvaccination\(^1,a\):**

- 98% efficacy against severe RGE (N=5,673: 2,834, vaccine; 2,839, placebo)
- 74% efficacy against mild, moderate, and severe RGE (N=5,673: 2,834, vaccine; 2,839, placebo)

* Study design: REST was a double-blind, placebo-controlled, randomized, multinational trial conducted from 2001 to 2004. Healthy infants 6 to 12 weeks of age were randomized to receive 3 oral doses of RotaTeq or placebo at 4- to 10-week intervals. The primary end point was safety with regard to intussusception, with nested adverse event and clinical efficacy substudies.\(^1\)

FDA=Food and Drug Administration; RGE=rotavirus gastroenteritis.

Selected Safety Information (continued)

Infants with Severe Combined Immunodeficiency Disease (SCID) should not receive RotaTeq. Post-marketing reports of gastroenteritis, including severe diarrhea and prolonged shedding of vaccine virus, have been reported in infants who were administered RotaTeq and later identified as having SCID.

Infants with a history of intussusception should not receive RotaTeq.

No safety or efficacy data are available from clinical trials regarding the administration of RotaTeq to infants who are potentially immunocompromised.
Selected Safety Information (continued)

In a post-marketing observational study in the US, cases of intussusception were observed in temporal association within 21 days following the first dose of RotaTeq, with a clustering of cases in the first 7 days.

No safety or efficacy data are available for administration of RotaTeq to infants with a history of gastrointestinal disorders.

Vaccine virus transmission from vaccine recipient to nonvaccinated contacts has been reported. Caution is advised when considering whether to administer RotaTeq to individuals with immunodeficient contacts.

In clinical trials, the most common adverse events included diarrhea, vomiting, irritability, otitis media, nasopharyngitis, and bronchospasm.

In post-marketing experience, intussusception (including death) and Kawasaki disease have been reported in infants who have received RotaTeq.

RotaTeq may not protect all vaccine recipients against rotavirus.

Please see the adjacent Brief Summary of the Prescribing Information.

**RotaTeq®**
*(Rotavirus Vaccine, Live, Oral, Pentavalent)*

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**DOSE AND ADMINISTRATION**

**FOR ORAL USE ONLY. NOT FOR INJECTION.** The vaccination series consists of three ready-to-use liquid doses of RotaTeq administered orally starting at 6 to 12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals. The third dose should not be given after 32 weeks of age.

**CONTRAINDICATIONS**

A demonstrated history of hypersensitivity to any component of the vaccine. Infants who develop fever or suggestive of hypogammaglobulinemia after receiving a dose of RotaTeq should not receive further doses of RotaTeq.

Infants with Severe Combined Immunodeficiency Disease (SCID) should not receive RotaTeq. Post-marketing reports of gastroenteritis, including severe diarrhea and prolonged shedding of vaccine virus, have been reported in infants who were administered RotaTeq and later identified as having SCID.

Infants with a history of intussusception should not receive RotaTeq.

**WARNINGS AND PRECAUTIONS**

Managing Allergic Reactions: Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

Immunocompromised Populations: No safety or efficacy data are available from clinical trials regarding the administration of RotaTeq to infants who are potentially immunocompromised including: Infants with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; Infants on immunosuppressive therapy (including high-dose systemic corticosteroids). RotaTeq may be administered to infants who are being treated with topical corticosteroids or inhaled steroids; Infants with primary and acquired immunodeficiency states, including HIV/AIDS or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. There are insufficient data from the clinical trials to support administration of RotaTeq to infants with indeterminate HIV status who are born to mothers with HIV/AIDS; Infants who have received a blood transfusion or blood products, including immunoglobulins within 42 days.

Vaccine virus transmission from vaccine recipient to non-vaccinated contacts has been reported.

Intussusception: Following administration of a previously licensed live rhesus rotavirus reagentant vaccine, an increased risk of intussusception was observed. In a post-marketing observational study in the US cases of intussusception were observed in temporal association within 21 days following the first dose of RotaTeq, with a clustering of cases in the first 7 days.

In worldwide passive-post-marketing surveillance, cases of intussusception have been reported in temporal association with RotaTeq.

Gastrointestinal Illness: No safety or efficacy data are available for administration of RotaTeq to infants with a history of gastrointestinal disorders including infants with active acute gastrointestinal illness, infants with chronic diarrhea and failure to thrive, and infants with a history of congenital abdominal disorders, and abdominal surgery. Caution is advised when considering administration of RotaTeq to these infants.

Shedding and Transmission: Shedding of vaccine virus was evaluated among a subset of subjects in REST4 4 to 6 days after each dose and among all subjects who submitted a stool antigen rotavirus positive sample at any time. RotaTeq was shed in the stools of 32 of 36 (8.9%, 95% CI (6.2, 12.3)) vaccine recipients tested after dose 1, 0 of 249 [0.0%, 95% CI (0.0%, 1.5%)] vaccine recipients tested after dose 2; and in 1 of 385 [0.3%, 95% CI (<0.1%, 1.4%)] vaccine recipients after dose 3. In phase 3 studies, shedding was observed as early as 1 day and as late as 15 days after a dose. Transmission of vaccine virus was not evaluated in phase 3 studies. Transmission of vaccine virus strains from vaccinees to non-vaccinated contacts has been observed post-marketing. The potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting natural rotavirus. Caution is advised when considering whether to administer RotaTeq to individuals with immunodeficient close contacts such as: individuals with malignancies or who are otherwise immunocompromised; individuals with primary immunodeficiency; or individuals receiving immunosuppressive therapy.

Febrile Illness: Febrile illness may be reason for delaying use of RotaTeq except when, in the opinion of the physician, withholding the vaccine entails a greater risk. Low-grade fever (<100.5°F [38.1°C]) itself and mild upper respiratory infection do not preclude vaccination with RotaTeq.

Incomplete Regimen: The clinical studies were not designed to assess the level of protection provided by only one or two doses of RotaTeq.

Limitations of Vaccine Effectiveness: RotaTeq may not protect all vaccine recipients against rotavirus.

Post-Exposure Prophylaxis: No clinical data are available for RotaTeq when administered after exposure to rotavirus.

**ADVERSE REACTIONS**

Clinical Studies Experience: 71,725 infants were evaluated in 3 placebo-controlled clinical trials including 36,168 infants in the group that received RotaTeq and 35,560 infants in the group that received placebo. Parents/guardians were contacted on days 7, 14, and 42 after each dose regarding intussusception and any other serious adverse events. The racial distribution was as follows: White (69% in both groups); Hispanic-American (14% in both groups); Black (8% in both groups); Multiracial (5% in both groups); Asian (2% in both groups); Native American (RotaTeq 2%, placebo 1%); and Other (<1% in both groups). The gender distribution was 51% male and 49% female in both vaccination groups. Because clinical trials are conducted under conditions that may not be typical of those observed in clinical practice, the adverse reaction rates presented below may not be reflective of those observed in clinical practice.

Serious Adverse Events: Serious adverse events occurred in 2.4% of recipients of RotaTeq when compared to 2.6% of placebo recipients within the 42-day period of a dose in the phase 3 clinical studies of RotaTeq. The most frequently reported serious adverse events for RotaTeq compared to placebo were: bronchiolitis (0.6% RotaTeq vs. 0.7% Placebo), gastroenteritis (0.2% RotaTeq vs. 0.3% Placebo), pneumonia (0.2% RotaTeq vs. 0.2% Placebo), fever (0.1% RotaTeq vs. 0.1% Placebo), and urinary tract infection (0.1% RotaTeq vs. 0.1% Placebo).

Deaths: Across the clinical studies, 52 deaths were reported. There were 26 deaths in the RotaTeq recipients compared to 27 deaths in the placebo recipients. The most commonly reported cause of death was sudden infant death syndrome, which was observed in 8 recipients of RotaTeq and 9 placebo recipients.

Intussusception: In REST, 34,837 vaccine recipients and 34,788 placebo recipients were monitored by active surveillance to identify potential cases of intussusception at 7, 14, and 42 days after each dose, and every 6 weeks thereafter for 1 year after the first dose. For the primary safety outcome, cases of intussusception occurring within 42 days of any dose, there were 6 cases among RotaTeq recipients and 5 cases among placebo recipients (see Table 1). The data did not suggest an increased risk of intussusception relative to placebo.

Table 1: Confirmed cases of intussusception in recipients of RotaTeq as compared with placebo recipients during REST

<table>
<thead>
<tr>
<th>RotaTeq (n=34,837)</th>
<th>Placebo (n=34,788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed intussusception cases within 42 days of any dose</td>
<td>6</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.6 (0.4, 6.4)</td>
</tr>
<tr>
<td>Confirmed intussusception cases within 365 days of dose 1</td>
<td>13</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.9 (0.4, 1.9)</td>
</tr>
</tbody>
</table>

*Relative risk and 95% confidence interval based upon group sequential design stopping criteria employed in REST.*

Among vaccine recipients, there were no confirmed cases of intussusception within the 42-day period after the first dose, which was the period of highest risk for the rhesus rotavirus-based product (see Table 2).

Table 2: Intussusception cases by day range in relation to dose in REST

<table>
<thead>
<tr>
<th>Day Range</th>
<th>RotaTeq</th>
<th>Placebo</th>
<th>RotaTeq</th>
<th>Placebo</th>
<th>RotaTeq</th>
<th>Placebo</th>
<th>RotaTeq</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1-14</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1-21</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1-42</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

All of the children who developed intussusception recovered without sequelae with the exception of a 9-month-old male who developed intussusception 98 days after dose 3 and died of post-operate sepsis. There was a single case of intussusception among 2,470 recipients of RotaTeq in a 7-month-old male in the phase 1 and 2 studies (716 placebo recipients).

Hematochezia: Hematochezia reported as an adverse experience occurred in 0.6% (398,130) of vaccine and 0.6% (345,560) of placebo recipients within 42 days of any dose. Hematochezia reported as a serious adverse experience occurred in <0.1% (403,150) of vaccine and <0.1% (725,536) of placebo recipients within 42 days of any dose.

*Rotavirus Efficacy and Safety Trial.*
Seizures: All seizures reported in the phase 3 trials of RotaTeq (by vaccination group and interval after dose) are shown in Table 3.

Table 3: Seizures reported by day range in relation to any dose in the phase 3 trials of RotaTeq

<table>
<thead>
<tr>
<th>Day range</th>
<th>1-7</th>
<th>1-14</th>
<th>1-42</th>
</tr>
</thead>
<tbody>
<tr>
<td>RotaTeq</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Placebo</td>
<td>15</td>
<td>8</td>
<td>24</td>
</tr>
</tbody>
</table>

Seizures were reported as serious adverse experiences occurred in <0.1% (27/36,150) of vaccine and <0.1% (18/35,536) of placebo recipients (not significant). Ten female seizures were reported as serious adverse experiences; 5 were observed in vaccine recipients and 5 in placebo recipients.

Kawasaki Disease: In the phase 3 clinical trials, infants were followed for up to 42 days of vaccine dose. Kawasaki disease was reported in 5 of 36,150 vaccine recipients and in 1 of 35,536 placebo recipients with an adjusted relative risk of 4.9 (95% CI 1.6, 23.9).

Most Common Adverse Events

Solicited Adverse Events: Detailed safety information was collected from 11,711 infants (6,138 recipients of RotaTeq) which included a subset of subjects in REST and all subjects from Studies 007 and 009 (Detailed Safety Cohort). A Vaccination Report Card was used by parents/guardians to record their child’s temperature and any episodes of diarrhea and vomiting on a daily basis during the first week following each vaccination. Table 4 summarizes the frequencies of these adverse events and irritability.

Table 4: Solicited adverse experiences within the first week after doses 1, 2, and 3 (Detailed Safety Cohort)

<table>
<thead>
<tr>
<th>Adverse experience</th>
<th>RotaTeq</th>
<th>Placebo</th>
<th>RotaTeq</th>
<th>Placebo</th>
<th>RotaTeq</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>n=5,616</td>
<td>n=5,077</td>
<td>n=5,215</td>
<td>n=4,725</td>
<td>n=4,885</td>
<td>n=4,382</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17.1%</td>
<td>16.2%</td>
<td>20.0%</td>
<td>19.4%</td>
<td>18.2%</td>
<td>17.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.7%</td>
<td>5.4%</td>
<td>5.0%</td>
<td>4.4%</td>
<td>3.6%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Irritability</td>
<td>7.1%</td>
<td>17.1%</td>
<td>6.0%</td>
<td>6.5%</td>
<td>4.3%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

Post-Marketing Experience: The following adverse events have been identified during post-approval use of RotaTeq from reports to the Vaccine Adverse Event Reporting System (VAERS). Reporting of adverse events following immunization to VAERS is voluntary, and the number of doses of vaccine administered is not known; therefore, it is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to vaccine exposure using VAERS data. In post-marketing experience, the following adverse events have been reported following the use of RotaTeq: Immune system disorders—Anaphylactic reaction. Gastrointestinal disorders—Intussusception (including death). Hematocytosis, Gastroenteritis with vaccine viral shedding in infants with Severe Combined Immunodeficiency Disease (SCID). Skin and subcutaneous tissue disorders—Urticaria, Angioedema. Infections and infestations—Kawasaki disease, Transmission of vaccine virus strains from vaccine recipient to non-vaccinated contacts.

Reporting Adverse Events: Parents or guardians should be instructed to report any adverse reactions to their health care provider. Health care providers should report all adverse events to the US Department of Health and Human Services’ Vaccine Adverse Event Reporting System (VAERS). VAERS accepts all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1988. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967 or report online to www.vaers.hhs.gov.

DRUG INTERACTIONS

Immunosuppressive therapies including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines.

Concomitant Vaccine Administration: In clinical trials, RotaTeq was administered concomitantly with diphtheria and tetanus toxoids and acellular pertussis (DTaP), inactivated poliovirus vaccine (IPV), H. influenzae type b conjugate (HiB), hepatitis B vaccine, and pneumococcal conjugate vaccine. The safety data available are in the ADVERSE REACTIONS section. There was no evidence for reduced antibody responses to the vaccines that were concomitantly administered with RotaTeq.

USE IN SPECIFIC POPULATIONS

Pediatric Use: Safety and efficacy have not been established in infants less than 6 weeks of age or greater than 32 weeks of age. Data are available from clinical studies to support the use of RotaTeq in pre-term infants according to their age in weeks since birth. Data are available from clinical studies to support the use of RotaTeq in infants with controlled gastroesophageal reflux disease.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: RotaTeq has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

PATIENT COUNSELING INFORMATION

Information for Parents/Guardians: Parents or guardians should be given a copy of the required vaccine information and be given the “Patient Information” appended to the prescribing information. Parents and/or guardians should be encouraged to read the patient information that describes the benefits and risks associated with the vaccine and ask any questions they may have during the visit.

For more detailed information, please read the Prescribing Information.

USPI-V280-0S-1411R021 Revised: 11/2014
means Purdue will be reaping greater revenues and OxyContin will not face patent competition for a longer amount of time,” Alexander says.

According to a 2012 report on CBS News, Purdue would receive a 6-month patent extension upon the completion of its study on children, which the company said it would add to the patents expiring in 2025 for newer formulations of the drug.5

**Addiction and children**

Levy says that, as an addiction specialist, the problem she sees most commonly is that kids use opioids because they’re available. “[I]t is the ‘reservoir’ of pain medications sitting in people’s medicine cabinets that seems to drive the epidemic,” she says. “We need to reduce the reservoir by prescribing more prudently and educating our patients about how to get rid of extra medication and the risks of leaving unused medications around. Pediatricians play a role in that—especially the education piece—but the large majority of the reservoir comes from prescriptions that were given to adult patients, and limiting prescribing to children is not likely to make much of a difference.”

Screening can play a part in preventing addiction that results from OxyContin prescribing, Levy notes. “From where I sit, opioid addiction is the end of a long road that nearly always starts with marijuana, alcohol, and/or tobacco use,” she says. “Of course not all kids who use marijuana or other drugs will go on to develop an opioid use disorder, but nearly all kids that develop an opioid use disorder start with some other substance. So, we need to screen routinely and deliver advice that not using is best for health.”

This screening is especially important before prescribing opioids because there is data suggesting that use of other substances, particularly marijuana, may “prime” the brain to be more vulnerable to opioid use disorders, Levy explains.6 “We want to take extra precaution with kids who have started using,” she says.

In addition, Levy points out that there have been studies showing that early exposure to opioids, even when used appropriately, increases the risk of later opioid use disorder.7 “So clearly we want to be careful with these medications and use them only when they are truly indicated, and when we do use them, we need to monitor to insure we are giving an appropriate dose and for an appropriate length of time,” she says.

Kolodny, who sees adolescent patients who are opioid addicted, says young people are becoming opioid addicted in 3 ways. One route is through nonmedical use, or recreational use, and he agrees that the drugs most often come from somebody’s medicine chest. Another route for young people to become addicted is through medical treatment, via iatrogenic addiction. “It’s hard for a person to be put on long-term opioids and not get addicted. I think if you could find some of the children who participated in these clinical trials, there’s a good likelihood that some of the children who participated are now addicted,” he notes.

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**More than 6% of children from 12 to 17 years of age have engaged in nonmedical opioid use in the past year, according to federal estimates.**


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**Senate passes the Comprehensive Addiction and Recovery Act authorizing creation of educational and recovery programs to address the opioid epidemic and directs the US Department of Health and Human Services to develop best practices for pain management and prescribing pain medication.**
The third route, which may be more common, is a little of both—a young person who gets exposed to an opioid medically, for wisdom teeth, sports injury, or some kind of surgical procedure. If that patient likes the effect of the opioid and no longer fears, Kolodny says that’s the perfect storm for later recreational use and subsequent addiction.

Best Rx practices
Of concern is that many physicians report they’re not confident about how to safely prescribe opioids. The truth is that OxyContin is a rare consideration for the community pediatrician, according to Neville. “This is not for a toothache or a sprained ankle or common ailments. This is for kids with sickle cell disease or cancer—most likely patients who are otherwise going to be seeing a specialist,” she says. Pediatricians need to know how opioid analgesics should be considered in pediatric patients when other drugs fail to sufficiently manage patients’ pain.

Warnings and precautions for pediatric patients taking OxyContin are the same as for adults. Every physician prescribing OxyContin to children and adolescents should use the lowest dose for the shortest amount of time, Neville advises. Also, don’t dispense a lot of pills; rather, dispense a reasonable amount that won’t end up as extra pills in the medicine cabinet, she says.

Careful prescribing includes careful monitoring as patients wean off the drug, cautions Neville. “For the general pediatrician, it’s like any drug; you should be educated on drugs you are prescribing. So, if you’re prescribing this drug, you should know the appropriate patient population and if a patient should be closely followed,” she says. “This is not an appropriate drug for short-term resolving of acute pain. Never has been.”

For references, go to ContemporaryPediatrics.com/
OxyContin-labeling

MARCH 16, 2016
CDC publishes Guidelines for Prescribing Opioids for Chronic Pain, providing recommendations for primary-care clinicians.

Medical waste removal has cost physicians thousands of dollars over the year with the charges going up every year and their business having nothing to show for their expense. There is now a cost-effective, professionally recognized alternative.

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A Pediatric Orthopedist’s Perspective

Opioids overshadow athletic injuries

STACY FRYE, MD

In my practice, we are seeing patients and their families being increasingly interested in gaining a competitive edge with regard to athletics. The off-season or dedicated rest period for many of our athletes is becoming obsolete. Children are training year-round, specializing in a single sport earlier on, and oftentimes playing for multiple teams at the same time in order to get ahead or even just keep up with their peers. One of the consequences of this is that our young athletes are running themselves down—pushing to be the best—at the cost of wear and tear on their bodies. Repetitive stress, fatigue, and poor technique lead to children suffering overuse injuries and put kids at risk for traumatic injury.

We see that the desire to compete and the pressure to stay in the game influence families’ decisions when it comes to participation and treatment. We often hear of the athlete who has an upcoming showcase for college scouts, a play-off game, a huge tournament, or a big tryout for which they “can’t” stop training. A patient may have been pushing through pain for months or for multiple sports seasons, but they will present to the office seeking a quick solution, often in the form of pain-relief medication. Although most people take prescription medications appropriately, studies have shown that about 20% of young persons aged 12 to 17 years have used prescription drugs for nonmedical reasons.1

Most opioids are not necessary

The reality is that the vast majority of our young athletes do not require strong painkillers for athletic injuries, and most can be managed with nonsteroidal anti-inflammatory medication. Stronger painkillers, such as opioids, may offer quick relief, consistent with the immediate-gratification mentality of our society: I want it now, fix it now, be stronger now. Our athletes want to be bigger, faster, stronger, and pain-free now.

Consider the old adage “no pain, no gain.” This mentality continues to be taught to young athletes as they are encouraged to play through pain and prove their strength both mentally and physically. The internal and external pressure to compete and stay in the game overshadows the risk of taking pain medication, including opioids. Although the painkiller can temporarily eliminate the pain, we need to remember—as prescribers and as educators to the family—that it does not eliminate the injury. The opioid does not quicken healing.

Opioid medications, such as oxycodone, morphine, hydromorphone, fentanyl, and codeine, are narcotic drugs used for moderate or severe pain relief. Prescription of opioid analgesics has increased over the last 20 years. Research has shown that exposure to prescription opioids ranges from 22% to 45% in US high school students.2 Adolescents in higher-impact sports such as football and wrestling have the highest severe injury rates3 and are more likely to be given prescription pain medications.4 However, exposure does not necessarily lead to misuse. A recent study in Pediatrics showed that daily

12% of male athletes and 8% of female athletes have used prescription opioids in a 12-month period.


FDA announces changes to class-wide safety labeling for immediate-release opioids, including a boxed warning to inform patients about the risks of misuse, abuse, addiction, overdose, and death. Also includes a precaution that maternal use during pregnancy can result in neonatal opioid withdrawal syndrome.
clinical feature

participation in sports and exercise is likely a protective factor with respect to opioid misuse and risk of lifetime heroin use (using opioids as a gateway drug).5

Unfortunately, there is no way to determine the absolute risk of a patient becoming addicted to medication, misusing it, or abusing it. However, screening for a history of drug abuse and the presence of risk factors can help the community pediatrician in deciding what type of medication may be most appropriate for a patient’s pain.

Assess risks before prescribing opioids

The Institute for Clinical Systems Improvement (ICSI) Acute Pain Assessment and Opioid Prescribing Protocol suggests assessing risks with the "ABCDPQRS" mnemonic:6

- Alcohol exposure;
- Benzodiazepines and other drug use;
- Clearance of the medication (any renal or hepatic issues);
- Delirium;
- Psychiatric comorbidities (personal and family);
- Query a prescription monitoring program;
- Respiratory issues; and
- Safety issues, because opioids are a controlled substance and there are dangers of driving or working while taking these medications.

The protocol is suggested for adult patients; however, its recommendations are helpful for any primary care provider, including suggestions for brief and comprehensive pain assessments, duration of treatment, and suggestions for how to answer difficult questions, explain addiction risk, and more.

Discussion and shared decision making are critical. The patient and family need to be educated on the risks of opioid medication, even when using short term. Informed decision making as a team, including the patient, physician, and parents, provides education regarding the specific medication prescribed, the expected benefit of the medication, possible adverse effects, and the suspected time for injury recovery. Warning signs that would require immediate medical attention need to be clearly stated.

I find it helpful to provide a brief information sheet so that the family can review what has been discussed after leaving the office and have it as a reference if any concerns arise. Additional helpful resources for parents are available at the Partnership for Drug-Free Kids website (www.drugfree.org/resources), including free e-books and fact sheets (such as Preventing Teen Abuse of Prescription Drugs).

Education is the key to prevent harm

Our current medical system puts pressure on physicians to see more patients and oftentimes does not allocate much time for patient and family education. However, it is crucial that we do not give in and just write a quick prescription to “fix” the pain and send these patients on their way. Consider that masking the pain is a ticket to play for some, meaning: The pain is gone. I feel good. I can play tonight. However, the injury is still there. He or she may not “feel it,” but the player with the torn anterior cruciate ligament (ACL), for example, is still playing with the torn ACL.

As physicians, we certainly have a desire to relieve suffering and help our patients, but our oath of “do no harm” must be paramount. We owe it to our patients to educate them regarding adverse effects, the risk of addiction, the potential harm of masking pain, and playing with injury. Whereas we all want to please our patients and satisfy our families, overprescribing painkillers is a real issue that we are seeing not only in the urban environment but very commonly in suburban and rural communities.

US BABIES BORN IN 2013 ADDICTED TO OPIOIDS:

6.0 PER 1000 HOSPITAL BIRTHS

—Centers for Disease Control and Prevention, August 12, 2016.

CONTINUED ON PAGE 54
clinical feature

CONTINUED FROM PAGE 17

Current research is, in part, aimed at finding more optimal strategies for analgesia and sedation that could be used in place of midazolam. According to the senior author of the study, Steven Miller, MD, further prospective long-term studies in multiple NICUs need to be performed to determine how the current neonatal analgesic and sedative practices impact functional outcomes.

“There is a growing recognition that pain and stress during neonatal intensive care predicts less robust brain development in the preterm neonate. So it is imperative that we find ways to minimize the pain and stress, and to identify ways of caring for the preterm neonate that promote optimal brain development,” says Miller, senior scientist and head, Division of Neurology, SickKids, and professor, Department of Paediatrics, University of Toronto, Ontario, Canada.

The findings of this study appear to caution against the use of midazolam in very preterm neonates, Miller says, especially those not undergoing surgery. Fortunately, the variability in sedative and narcotic use across NICUs suggests that alternatives are available, but care should be individualized for each patient.

In addition to the heightened awareness of the importance to prevent pain and ameliorate stress, Miller says that there is a trend in Canadian NICUs to promote nonpharmacologic management of pain and stress in preemies, such as skin-to-skin contact, bundling, nonnutritive sucking, and kangaroo care.

“Our challenge is how to identify which pharmacological and nonpharmacological strategies provide effective analgesia and sedation, while promoting optimal brain development. Pain and stress in preterm babies are of significant concern for families and healthcare providers in the NICU. We should be doing all we can to prevent pain and stress in the preterm neonate to promote their brain health and support their families,” Duerden says.

Dr Petrou is a freelance medical writer based in Budapest, Hungary. He has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

REFERENCE

CONTINUED FROM PAGE 26

approximately 80 to 100 times more potent than morphine on a weight-per-weight basis. The recent combination of fentanyl with or substitution for heroin in the illicit drug culture is believed to have led to the uptick in illicit fentanyl-related deaths because of the drug’s much higher potency and mode of administration. The interest of a higher potency drug such as fentanyl in the drug abuse community presents a difficult problem, as users are drawn to the “stronger” product despite the dangerous adverse effects.

“In anesthesia or emergency medicine, drugs like fentanyl are administered by medical professionals in a controlled setting. This picture is very different among drug abusers, which likely plays a part in the increase seen in illicit fentanyl-related deaths,” Spiller says.

The current study included 2 infants who had unfortunately ingested their parents’ fentanyl-laced heroin. Drug abuse is not solely seen in adults, Spiller says, and it is not an uncommon problem in adolescents aged 15 to 17 years. According to Spiller, clinicians should be wary when managing this patient population, and ensure that they receive appropriate education in the lethal adverse effects of illicit fentanyl.

“Fentanyl is a wholly different drug and it is not just because of its potency. A striking number of deaths were noticed after it came to the illicit drug market. The danger of sudden chest wall rigidity following illicit fentanyl abuse is very real and we need to educate this population accordingly, which could include concerted efforts from clinicians, public health institutions, as well as rehab group counselors,” Spiller says.

Dr Petrou is a freelance medical writer based in Budapest, Hungary. He has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

REFERENCE
Peeling rash in a 4-year-old boy

KELLY SCHERMER, BS, MPH, MS3; LISA GWYNN, DO, MBA

THE CASE

The mother of a 4-year-old boy, whose family recently emigrated from Haiti, brings him to the pediatric mobile clinic for evaluation of a rash that had begun 11 days earlier as an eruption of vesicular, pruritic papules on the bilateral lower extremities and had spread to the buttocks and medial thighs with sparing of the face. The skin eruption was followed by desquamation of the skin on his palms and soles.
Prodromal symptoms included 3 days of nasal congestion, rhinorrhea, and subjective fever. The patient’s past medical history was significant for childhood obesity.

Initial physical exam revealed symmetric, diffuse, 2-mm to 4-mm grey-brown flat-topped papules with subtle surrounding desquamation that extended from the hands and feet centrally, including medial thigh, buttocks, and occasional lesions on the torso (Figures 1 and 2). The palms and soles exhibited peeling of the superficial layers of skin, revealing raw, mildly erythematous tissue (Figure 3). No oral lesions or exudates, conjunctivitis, or lymphadenopathy were noted, and the remainder of the examination was noncontributory.

**Differential diagnosis**

Despite an extensive list of acute childhood exanthems, the possible etiologies of fever and rash in the patient were narrowed down to hand-foot-mouth disease (HFMD), varicella, post-streptococcal rash, and herpes simplex virus (HSV). (See Table.1-3)

The index of suspicion was highest for HFMD, a viral exanthem most commonly caused by coxsackievirus A16 (CVA16) and enterovirus 71 (EV71). Classic HFMD is characterized by fatigue, sore throat/mouth, and a typical cutaneous eruption most significant on the palms, soles, and distal extremities. It most commonly affects preschool-aged children with the highest incidence rates during the summer and fall in temperate climates. Ulcerative lesions initially appear on the buccal mucosa and hard palate following a prodrome of fever, muscle aches, and fatigue. Several days later one will notice the development of vesicles on the hands, feet, extremities, and buttocks that can be painful and itchy. The patient exhibited the classic skin findings of HFMD; however, he denied a sore throat, and no ulcerative lesions were noted on the oral mucosa. Yet, the lack of an oral exanthem did not rule out the diagnosis of HFMD as cases presenting with solely cutaneous findings have been reported in the literature.4

Varicella, more commonly known as chicken pox, begins with a low-grade fever and fatigue, followed by the development of an intensely pruritic rash characterized by little fluid blisters on a red base (“dew drops on a rose petal”).1 The rash usually starts on the face and trunk, eventually spreading to the arms and legs with involvement of mucous membranes as well. Lesions are often found in various stages as new crops of vesicles erupt and crust over in successive pattern every few days. Initial concern for varicella was heightened because the patient was unimmunized upon arrival to the United States and had received only the first dose of the varicella vaccine series less than 5 months prior to rash onset. At the time of his sick visit, he was due for his second catch-up dose; however, the decision was made to withhold required vaccinations until the rash improved. Despite the patient’s vaccination status, inoculation with varicella was unlikely in this patient given the location, pattern, and spread of the lesions. He also exhibited extensive involvement of the palms and soles with sparing of the trunk and face, which is uncommon for varicella.

Scarlet fever is a childhood exanthem that results from infection with group A beta-hemolytic streptococci. It is characterized by pharyngitis, fever, and a typical rash on the trunk and extremities. The rash begins as a maculopapular eruption on the neck and upper chest, spreading to the torso and extremities. It is typically associated with a strawberry tongue, pharyngeal exudate, and tonsillitis. Scarlet fever is usually caused by group A beta-hemolytic streptococci, although cases associated with group A streptococci have been reported. Scarlet fever is typically self-limiting and resolves within 5 to 7 days. However, complications such as acute rheumatic fever or glomerulonephritis may occur in a small percentage of cases.

**Comparison of differential diagnoses**

- **Hand-foot-mouth disease (HFMD):**
  - Characterized by symmetric, diffuse, 2-mm to 4-mm grey-brown flat-topped papules with subtle surrounding desquamation.
  - Extends from the hands and feet centrally, including medial thigh, buttocks, and occasional lesions on the torso.
  - No oral lesions or exudates, conjunctivitis, or lymphadenopathy.
  - Classic skin findings of HFMD.

- **Varicella (Chicken Pox):**
  - Begins with a low-grade fever and fatigue.
  - Followed by the development of an intensely pruritic rash characterized by little fluid blisters on a red base.
  - Starts on the face and trunk, eventually spreading to the arms and legs.
  - May involve mucous membranes.

- **Scarlet Fever:**
  - Characterized by pharyngitis, fever, and a typical rash on the trunk and extremities.
  - Typically associated with a strawberry tongue, pharyngeal exudate, and tonsillitis.
  - Caused by group A beta-hemolytic streptococci.

**Conclusion**

The patient exhibited the classic skin findings of HFMD; however, he denied a sore throat, and no ulcerative lesions were noted on the oral mucosa. The lack of an oral exanthem did not rule out the diagnosis of HFMD. Despite the patient’s vaccination status, inoculation with varicella was unlikely in this patient given the location, pattern, and spread of the lesions. He also exhibited extensive involvement of the palms and soles with sparing of the trunk and face, which is uncommon for varicella.

Scarlet fever is a childhood exanthem that results from infection with group A beta-hemolytic streptococci. It is typically self-limiting and resolves within 5 to 7 days. However, complications such as acute rheumatic fever or glomerulonephritis may occur in a small percentage of cases.
BESIVANCE® (besifloxacin ophthalmic suspension) 0.6% is a quinolone antimicrobial indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria:

- Aerococcus viridans
- Corynebacterium pseudodiphtheriticum
- Corynebacterium striatum
- Haemophilus influenzae
- Moraxella catarrhalis
- Moraxella lacunata
- Pseudomonas aeruginosa
- Staphylococcus aureus
- Staphylococcus epidermidis
- Staphylococcus hominis
- Staphylococcus lugdunensis
- Staphylococcus warneri
- Streptococcus mitis group
- Streptococcus oralis
- Streptococcus pneumoniae
- Streptococcus salivarius

*Efficacy for this organism was studied in fewer than 10 infections.

Important Safety Information about BESIVANCE®

- BESIVANCE® is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.
- As with other anti-infectives, prolonged use of BESIVANCE® may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy.
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE®.
- The most common adverse event reported in 2% of patients treated with BESIVANCE® was conjunctival redness. Other adverse events reported in patients receiving BESIVANCE® occurring in approximately 1-2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.
- BESIVANCE® is not intended to be administered systemically. Quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.
- Safety and effectiveness in infants below one year of age have not been established.

Please see brief summary of Prescribing Information on adjacent page.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary does not include all the information needed to use Besivance safely and effectively. See full prescribing information for Besivance.

Besivance® (besifloxacin ophthalmic suspension) 0.6%
Sterile topical ophthalmic drops
Initial: 2009

1 INDICATIONS AND USAGE
Besivance® (besifloxacin ophthalmic suspension) 0.6%, is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: Aerococcus viridans*, CDC coryneform group G, Corynebacterium pseudodiphtheritum*, Corynebacterium striatum*, Haemophilus influenzae, Moraxella catarrhalis*, Moraxella lacunata*, Pseudomonas aeruginosa*, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus hominis*, Staphylococcus lugdunensis*, Staphylococcus warneri*, Streptococcus mitis group, Streptococcus oralis, Streptococcus pneumoniae, Streptococcus salivarius*.

*Efficacy for this organism was studied in fewer than 10 infections.

2 DOSAGE AND ADMINISTRATION
Invert closed bottle and shake once before use.

Instill one drop in the affected eye(ies) 3 times a day, four to twelve hours apart for 7 days.

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS
5.1 Topical Ophthalmic Use Only
NOT FOR INJECTION INTO THE EYE.

Besivance is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

5.2 Growth of Resistant Organisms with Prolonged Use
As with other anti-infectives, prolonged use of Besivance (besifloxacin ophthalmic suspension) 0.6% may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

5.3 Avoidance of Contact Lenses
Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance.

6 ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with the rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Besivance in approximately 1,000 patients between 1 and 98 years old with clinical signs and symptoms of bacterial conjunctivitis.

The most frequently reported adverse reaction was conjunctival redness, reported in approximately 2% of patients.

Other adverse reactions reported in patients receiving Besivance occurring in approximately 1-2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Pregnancy Category C.

Oral doses of besifloxacin up to 1000 mg/kg/day were not associated with visceral or skeletal malformations in rat pups in a study of early-fetal development, although this dose was associated with maternal toxicity (reduced body weight gain and food consumption) and maternal mortality. Increased post-implantation loss, decreased fetal body weights, and decreased fetal ossification were also observed. At this dose, the mean Cmax in the rat dams was approximately 20 mcg/mL, >45,000 times the mean plasma concentrations measured in humans.

The No Observed Adverse Effect Level (NOAEL) for this embryo-fetal development study was 100 mg/kg/day (Cmax = 5 mcg/mL, >11,000 times the mean plasma concentrations measured in humans).

In a prenatal and postnatal development study in rats, the NOAEL for both fetal and maternal toxicity were also 100 mg/kg/day. At 1000 mg/kg/day, the pups weighed significantly less than controls and had a reduced neonatal survival rate. Atamitement of developmental landmarks and sexual maturation were delayed, although surviving pups were treatable by Besivance or other antibacterial drugs in the future.

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8.2 Lactation

The safety and effectiveness of Besivance® in infants below one year of age have not been established. The efficacy of Besivance in treating bacterial conjunctivitis in pediatric patients older than 1 year has been demonstrated in controlled clinical trials. See CLINICAL STUDIES (14).

There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

8.3 Nursing Mothers

Besifloxacin has been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when Besivance is administered to a nursing mother. It can be presumed to be excreted in human milk. Caution should be exercised when Besivance is administered to a nursing mother.

8.4 Pediatric Use

Pediatric use is not recommended. Adverse reactions found in anti-infective trials.

17 PATIENT COUNSELING INFORMATION

Patients should be advised to avoid contaminating the applicator tip with material from the eye, fingers or other sources.

Although Besivance is not intended to be administered systemically, quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.

Patients should be advised to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance.

Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance.

Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.

Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance.

Patients should be advised to thoroughly wash hands prior to using Besivance.

Patients should be advised to instruct and closed bottle (upside down) and shake once before each use. Remove cap with bottle still in the inverted position. Tilt head back, and with bottle inverted, gently squeeze bottle to instill one drop into the affected eye(s).

Manufactured by: Bausch & Lomb Incorporated

Tampa, Florida 33637

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U.S. Patent Nos. 6,685,958; 6,699,492; 5,447,926

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US/BES/15/0019

Based on 9142605(flat)-9142705(folded)
streptococci (GABHS) and subsequent release of a pyrogenic exotoxin.2 The prodrome consists of 1 to 2 days of fever and sore throat followed by the appearance of a generalized, erythematous, fine papular rash that is often referred to as sandpaper-like in texture. The rash typically begins on the trunk and then spreads throughout the body, often sparing the palms and soles. The rash begins to fade several weeks after onset and is followed by desquamation of the skin, this time including the palms and soles. This patient presented with extensive, painful desquamation of the hands and feet several weeks after his mother first noted the rash. However, the evidence against scarlet fever in the patient was stacked and included the fact that the rash was vesicular in nature, involved the palms and soles with sparing of the trunk face, and was pruritic.

First-episode oropharyngeal infection with HSV is commonly referred to as primary gingivostomatitis.3 Toddlers aged between 1 and 3 years are most commonly affected. Oral vesicular lesions typically develop following an average incubation period of 4 days and can be seen on the hard palate, tongue, gingiva, and around the lips. These fragile vesicles quickly rupture, leaving ulcers on an erythematous base. Other associated symptoms include fever, sore throat, anorexia, cervical adenopathy, drooling, and mucosal edema. If drooling is excessive, lesions may develop on the chin and neck as well. Generally a self-limiting illness, HSV infection lasts up to 3 weeks. Although the patient exhibited clusters of vesicular lesions similar in appearance to those of HSV, he had no evidence of oral or gingival involvement, making primary HSV infection highly unlikely. In laboratory testing, a rapid streptococcal A screen was ordered and returned positive.

**Dermatology consultation**

Dermatology was consulted, and 1 week later its report stated the “most likely” diagnoses of resolving viral exanthem with palmar and plantar desquamation/peeling and dry skin/xerosis (Figure 4). Dermatology recommended application of 2.5% hydrocortisone ointment to control the itching and emollient therapy. In addition, the mother was advised that the palms and soles would continue to desquamate as the rash resolved. Follow-up in 2 weeks was recommended.

**Course of treatment**

Although the diagnosis of a viral exanthem was high on the differential diagnosis, because of the desquamation of the hands and feet and the positive rapid strep screen, the patient was treated with a 10-day course of amoxicillin. However, the positive rapid strep test might have served as a marker of colonization in the patient. In this case, the peeling might have been related to the widespread primary viral lesions on the distal extremities and unrelated to streptococcal infection.

Although there was clinical debate as to the possibility that the patient could be a chronic GABHS carrier, it was decided to proceed with treatment. The boy returned for a follow-up exam approximately

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**Differential Diagnosis for Rash and Fever**

<table>
<thead>
<tr>
<th>Location/Mouth disease</th>
<th>Location</th>
<th>Appearance</th>
<th>Helpful Hints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-foot-mouth disease</td>
<td>Hands, feet, buttocks, oral cavity</td>
<td>Lesions initially appear vesicular then ulcerate</td>
<td>Peak incidence in summer and autumn</td>
</tr>
<tr>
<td>Varicella</td>
<td>Begins on face, spreads to trunk and extremities</td>
<td>Vesicles on an erythematous base: “Dew drops on a rose petal”</td>
<td>Highly pruritic Polymorphic eruptions appear in different stages of evolution</td>
</tr>
<tr>
<td>Scarlet fever</td>
<td>Begins on upper trunk, then spreads to face and extremities with sparing of the palms and soles</td>
<td>Erythematous blanching macules and sandpaper-like papules</td>
<td>Exudative pharyngitis, palatal petechiae, abdominal pain</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Orolabial, including hard palate, tongue, and gingiva</td>
<td>Vesicular lesions that rapidly rupture, leaving shallow ulcers on an erythematous base</td>
<td>Gingivitis, sore throat, increased drooling</td>
</tr>
</tbody>
</table>

---

2 weeks after the initial presentation. Reevaluation of his skin revealed numerous macular hyperpigmented lesions over the lower and upper extremities with involvement of the buttocks and thighs. In addition, desquamation of the palms and soles with mild erythema was still evident. The patient no longer complained of pruritus or pain and the rash appeared to be resolving. No other significant findings were noted on physical exam. Throat culture performed at this visit was negative for GABHS. The parent was reassured that the rash would continue to resolve and no further treatment was necessary.

One month later, the patient’s concerned mother brought him back to the mobile clinic because she had made a troubling new finding: His nails had begun to fall off (Figure 5). Pertinent physical exam findings included desquamation of the nails on both the hands and toes as well as evidence of hyperpigmented macules of the bilateral lower and upper extremities. The macules were consistent with residual postinflammatory markings of a resolved exanthema (Figures 6 and 7).

Discussion
In the United States, CVA16 and EV71 are the most commonly implicated infectious agents associated with HFMD. Recently, however, atypical cases of HFMD linked to an uncommon strain of coxsackievirus, specifically CVA6, have been reported worldwide, initially in China and the far East. Atypical cases are characterized by unique clinical manifestations, such as extensive cutaneous disease variants, palmoplantar desquamation, and perioral lesions. Coxsackie A6 was initially discovered as the predominant virus responsible for an epidemic of HFMD in Finland and Singapore in 2008. Initial outbreak of CVA6 HFMD in the United States was not reported until 2012. The CVA6 subtype is characterized by unique dermatological findings, including delayed nail changes following the acute phase of the illness, less mucosal involvement, and widespread vesiculobullous eruption that extends beyond the typical palmar and plantar distribution of classic HFMD.

Nail desquamation, formally known as onychomadesis, is characterized by separation of the proximal nail plate from the matrix most commonly followed by eventual shedding from the base. Onychomadesis is associated with numerous conditions including Kawasaki disease, epidermolysis bullosa, and streptococcal infection; however, the most commonly implicated infectious etiology is HFMD. Although numerous serotypes of coxsackievirus are associated with onychomadesis, research suggests that CVA6 strain may be the major culprit. On average, nail findings become clinically evident at 4 to 10 weeks postinfection. There is no specific treatment for this condition and prognosis is good as eventual regrowth of nails occurs spontaneously in a vast majority of cases.

Because of the dermatologic findings and pattern of secondary sequelae from the initial presentation, as well as the positive GABHS test, the suspicion was high that this patient had a coinfection of GABHS and coxsackievirus. Very limited research exists on the clinical manifestations of coinfection with coxsackievirus and GABHS. A study conducted by Egyptian researchers nearly 30 years ago attempted to bridge the link between GABHS,
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FUNGAL INFECTIONS
HEALING
For the treatment of superficial skin infections caused by yeast (Candida albicans)

SOOTHING
Relief from burning, itching and discomfort

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TREATMENT
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PREVENTION
Use daily to prevent diaper rash

TRUSTED
Recommended by pediatricians, loved by parents

ECZEMA
HEALING
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SOOTHING
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MOISTURIZING
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coxsackie B virus (CBV), and rheumatic fever. The researchers postulated that CBV may serve as a cofactor in the development of rheumatic fever following infection with GABHS. Although they found that patients with acute rheumatic fever were more likely to be coinfected with CBV and GABHS versus GABHS alone, they failed to demonstrate a clinically significant correlation. Thorough literature review has failed to reveal any cases documenting the potential sequelae, particularly in regard to cutaneous manifestations of coinfection with GABHS and coxsackie A virus. More research is required to examine the role of GABHS serving as a cofactor for the development of more significant cutaneous disease.

Diagnosis, treatment, follow-up
Classic HFMD caused by CVA16 and EV17 was once the predominant presentation in pediatric offices across the United States. However, pediatricians are finding that the CVA6 presentation may be the new typical HFMD. Classic HFMD is primarily a clinical diagnosis because the disease presents with such a classic appearance and location of the cutaneous and oral lesions.

Primary care physicians generally diagnose the condition without confirmatory viral testing or dermatology consultation. However, given the rise in the atypical form of HFMD, it may be wise for clinicians to become familiar with laboratory techniques that allow for detection of the specific viral serotype, such as stool samples, throat swabs, and reverse transcription-polymerase chain reaction (RT-PCR) testing of vesicular fluid.

As of yet, no antiviral therapy has been developed for the treatment of HFMD. Supportive therapy, particularly hydration and pain control, is the treatment of choice as the disease is generally self-limited in nature. Strict adherence to hand hygiene protocols is imperative in limiting the spread of the virus and future inoculation as it is mainly transmitted via fecal-oral route.

Patient outcome
The patient has since returned to the clinic for routine vaccinations, at which point in time his nail findings had resolved and a point-of-care strep test was negative, thus eliminating the possibility that the patient was a carrier.

Ms Schermer is a third-year medical student at the University of Miami Leonard M. Miller School of Medicine, Miami, Florida. Dr Gwynn is assistant professor of Clinical Pediatrics and director of the pediatric mobile clinic at the University of Miami Leonard M. Miller School of Medicine, Florida. The authors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have interest in any part of this article.

REFERENCES
For references, go to ContemporaryPediatrics.com/puzzler-0916
POC influenza testing: State of the art

With point-of-care (POC) molecular assays, pediatricians can diagnose influenza A and B during the office visit.

Each year in the United States, seasonal flu is responsible for dozens of deaths and thousands of hospitalizations among children, especially those with underlying medical conditions. Rapid diagnosis identifies those children who would be candidates for antiviral therapy that can shorten the course of illness and lessen symptom severity. Until recently, rapid office tests for influenza have been very unreliable. With the introduction of point-of-care (POC) molecular assays, pediatricians can diagnose influenza A and B during the office visit with sensitivity and specificity comparable to reference assays.

This article will review influenza—its presentation, symptoms and treatment—and review the POC influenza tests currently available to help expedite diagnosis.

Influenza basics

The 2 influenza viruses that cause human epidemics are influenza A and B. Influenza A is categorized into subtypes based on hemagglutinin and neuraminidase protein antigens. Hemagglutinin is responsible for the entry of the virus into cells, while the neuraminidase facilitates the release of virus from host cells. Influenza B is not categorized into subtypes and is separated into 2 genetic lineages: Yamagata and Victoria.

The US Food and Drug Administration (FDA) has recommended that the 2016-2017 influenza trivalent vaccines used in the United States contain an A/California/7/2009 (H1N1) pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brussels/60/2008-like virus (B/Victoria lineage). It also recommends that quadrivalent vaccines, which have 2 influenza B viruses, contain the viruses recommended for the trivalent vaccines, as well as a B/Phuket/3073/2013-like virus (B/Yamagata lineage). This represents a change in the influenza A(H3N2) component and a change in the influenza B lineage included in the trivalent vaccine compared with the composition of the 2015-2016 influenza vaccines. As recently reported in the medical and popular press, the live attenuated influenza vaccine (LAIV) is not recommended for prophylaxis this season because of its lack of efficacy.

According to the American Academy of Pediatrics Committee on Infectious Diseases (aka, the Red Book), influenza viruses are spread through coughing and sneezing as well as with contact with respiratory droplets on surfaces. The incubation period for the disease is 1 to 4 days, and patients shed virus and are considered contagious for 1 day before symptoms begin and during the course of the illness.

Typically, influenza begins in November and lasts until May, with peak season usually from January to March each year. Symptoms include chills, fever, sore throat, headache, and cough, with myalgia being a very predominant symptom. It is estimated that 10% to 40% of children are infected in any given year. Children aged younger than 2 years and patients with an underlying medical condition are at particular risk of contracting severe
disease. High-risk patients include those having:1
- Asthma or other chronic pulmonary diseases, such as cystic fibrosis;
- Hemodynamically significant cardiac disease;
- Immunosuppressive disorders or therapy (see “Special Considerations,” Red Book, page 488);
- Human immunodeficiency virus (HIV) infection;
- Sickle cell anemia and other hemoglobinopathies;
- Diseases that necessitate long-term aspirin therapy, including juvenile idiopathic arthritis or Kawasaki disease;
- Chronic renal dysfunction;
- Chronic metabolic disease, including diabetes mellitus; and
- Any condition that can compromise respiratory function (eg, neurodevelopmental disorders, seizure disorders).

**Treatment options**
The Centers for Disease Control and Prevention (CDC) recommends antiviral treatment for high-risk patients, as well as for other patients “who in the view of their physician would benefit from treatment.” Antiviral therapy is most effective if started within 48 hours of symptom onset. Available antivirals include oral oseltamivir (Tamiflu) for patients as young as newborns; inhaled zanamivir (Relenza) for patients aged 7 years and older; and intravenous peramivir (Rapivab) for hospitalized patients aged 18 years and older who cannot take other antivirals (Table 13). These are neuraminidase inhibitors that prevent the release of virus from infected cells and reduce further infection. Neuraminidase inhibitors are effective against both influenza A and influenza B virus, and can be used for prophylaxis for patients who are high risk if they are exposed to individuals with influenza.3

**Diagnosing influenza: Then and now**
Lateral flow immunoassays for influenza first became available in 1998, with the first waived rapid flu test available in 2000. Over 21 million POC rapid tests for influenza are performed in the United States each year. This contrasts with about 50 million strep tests performed each year. These tests involve the extraction of viral nucleoprotein antigen from a swab, the placement of the extracted specimen into a test cartridge or onto a test strip, and the capturing of antigen by an antibody conjugated with a colored nanoparticle. As the antibody antigen complex migrates through the test system, it is captured by an antibody fixed onto the cartridge or strip, producing a colored line. Colored lines indicate the presence of influenza virus A or B and also indicate whether the test was performed correctly. Specimens that can be used with these tests include swabs obtained from the anterior nares, the nasopharynx, as well as from nasal aspirate or wash. Like all similar assays, positive and negative controls need to be run per the manufacturers’ recommendations, usually when an office receives a new shipment or a new lot number of test kits.

The CDC has cautioned physicians regarding the reliability of rapid antigen influenza tests, based on lateral flow immunoassay technology, because their sensitivities have been poor.4 A meta-analysis of more than 159 studies demonstrated a sensitivity of 64.6% for Influenza A and 52.2% for influenza B compared with reference assays.5 It should be recognized that physicians fare poorly in distinguishing patients with flu from those who do not, based on history and examination. A recent study showed that physicians working in an emergency department could only diagnose influenza in adult patients with a sensitivity of 36% when diagnosis was established with PCR testing.6 Helpful when positive, false negative tests are common with lateral flow immunoassay tests, thus negative tests do not exclude the disease. Reference assays for influenza include viral culture, which takes over a week to return, and reverse transcriptase polymerase chain reaction assay (RT-PCR), which can produce results within hours but is only available at reference labs, so specimens need to be sent out for testing, delaying...
diagnosis. Traditional lateral flow influenza A and B kits cost about $18 to $22 per test with reimbursements running approximately $16 per virus tested. Note that these are billed as 87804 each for both influenza A and influenza B testing, so 2 units of service are charged, bringing the reimbursement into the $32 range.

Newest rapid flu tests

Two new rapid influenza tests with improved sensitivities have appeared on the market over the past few years. These include the Veritor system from BD Diagnostics (Franklin Lakes, New Jersey) and the Sofia Influenza A+B FIA from Quidel (San Diego, California).

The Veritor system, combines a lateral flow immunoassay with an optical reader to detect “weak” positive rapid influenza A and B tests that would otherwise go undetected visually. This was introduced as a Clinical Laboratory Improvement Amendments (CLIA)-waived test for influenza in 2008. The reader costs $300, and the test sells for $16 per cartridge, which tests for both influenza A and B. The test is charged under the CPT code 87804. The specimen swab is placed in a tube containing extraction solution and then 3 drops of the solution are placed in the sample well in the cartridge. After 10 minutes, the cartridge is inserted into the optical reader, which then displays the results.

Another advantage of this test for pediatric patients is that the same specimen can be tested using another Veritor assay cartridge for respiratory syncytial virus (RSV). In young patients, RSV can produce pneumonia-like illnesses. Identifying patients with RSV can prevent the inappropriate use of antibiotics to treat a viral infection, whereas identifying influenza within 48 hours of symptom onset would merit consideration of antiviral medication to shorten the course of the illness.

Studies have shown that the Veritor influenza assay has a sensitivity of 90.2% for influenza A and 87.5% for influenza B. In addition, it can detect antigen with fewer viral particles present compared with lateral flow immunoassays. The Veritor system has a level of detection of 10^5 TCID50/ml (TCID 50/ml=tissue culture infectious dose; ie, dose of virus that will produce pathological change in 50% of cell cultures inoculated), better than those of lateral flow assays that usually are of the order of 10^6 TCID 50/ml.

The Sofia Influenza A+B FIA was introduced in 2011 and received CLIA-waived status in 2012. The test is a fluorescent immunoassay that involves an extraction and testing phase. Following a 1-minute extraction from a nasal swab, nasopharyngeal swab, or nasopharyngeal wash or aspirate, an aliquot of the specimen is dispensed into a testing cassette sample well. During the 15-minute test, the specimen migrates through a test strip containing various “chemical environments.” If influenza A or B antigens are present, they will be bound by antibodies coupled to fluorescent microparticles that migrate through the test membrane. The fluorescent microparticles containing bound antigen will be captured by antibodies on the test membrane where they are detected by the Sofia device.

The test has been shown to have sensitivities of 94% for influenza A and 89% for influenza B. The reader costs $4500 and each test costs about $16. As with the Veritor system, the same specimen can be used to test for both influenza and RSV with the Sophia device, with cartridges run simultaneously before insertion in the device.

Waived ‘molecular testing’ is available

Two POC tests are presently available from Alere (Waltham, Massachusetts) and Roche (Pleasanton,
### Table 1

<table>
<thead>
<tr>
<th>Antiviral Agent</th>
<th>Use</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oseltamivir</strong> (Tamiflu)</td>
<td>Treatment (5 d)</td>
<td>If aged &lt;1 y:\n 3 mg/kg/dose twice/d&lt;sup&gt;a,c&lt;/sup&gt;\n If aged ≥1 y, dose varies by child’s weight: &lt;br&gt;≤15 kg, dose is 30 mg twice/d &lt;br&gt;$&gt;$15 kg-23 kg, dose is 45 mg twice/d &lt;br&gt;$&gt;$23 kg-40 kg, dose is 60 mg twice/d &lt;br&gt;$&gt;$40 kg, dose is 75 mg twice/d</td>
<td>75 mg twice/d</td>
</tr>
<tr>
<td><strong>Chemoprophylaxis (7 d)</strong></td>
<td>If child is aged &lt;3 mo, use of oseltamivir for chemoprophylaxis is not recommended unless situation is judged critical due to limited data in this age group.\n If child is ≥3 mo and &lt;1 yr: &lt;br&gt;3 mg/kg/dose once/d&lt;sup&gt;b&lt;/sup&gt;\n If ≥1 y, dose varies by child’s weight: &lt;br&gt;≤15 kg, dose is 30 mg once/d &lt;br&gt;$&gt;$15 kg-23 kg, dose is 45 mg once/d &lt;br&gt;$&gt;$23 kg-40 kg, dose is 60 mg once/d &lt;br&gt;$&gt;$40 kg, dose is 75 mg once/d</td>
<td>75 mg once/d</td>
<td></td>
</tr>
<tr>
<td><strong>Zanamivir</strong> (Relenza)</td>
<td>Treatment (5 d)</td>
<td>10 mg (2 5-mg inhalations) twice/d (FDA approved and recommended for use in children aged ≥7 y)</td>
<td>10 mg (2 5-mg inhalations) twice/d</td>
</tr>
<tr>
<td><strong>Chemoprophylaxis (7 d)</strong></td>
<td>10 mg (2 5-mg inhalations) once/d (FDA approved for and recommended for use in children ≥5 y)</td>
<td>10 mg (2 5-mg inhalations) once/d</td>
<td></td>
</tr>
<tr>
<td><strong>Peramivir</strong> (Rapivab)</td>
<td>Treatment (1 d)</td>
<td>N/A (FDA approved and recommended for use in adults ≥18 y)</td>
<td>1 600-mg dose, via intravenous infusion for 15-30 min</td>
</tr>
<tr>
<td><strong>Chemoprophylaxis</strong></td>
<td>N/A (FDA approved and recommended for use in children ≥5 y)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

**Footnotes:**
- For footnotes, see the full article online at ContemporaryPediatrics.com/POC-flu-test
- Abbreviations: CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; N/A, not applicable.
- From: Centers for Disease Control and Prevention.2

California) that utilize nucleic acid amplification to detect influenza with sensitivities comparable to RT-PCR assays. In the near future, Cepheid (Sunnyvale, California) will release its own POC influenza waived test for its GeneXpert Xpress System. As noted in my previous Peds v2.0 article on disruptive technologies (Contemporary Pediatrics, July 2016), these devices are “game changers,” bringing diagnostic capability into the office on par with reference labs.

The **Alere i Influenza** device detects influenza A or B nucleic acid from nasal specimens using the company’s proprietary isothermal nucleic acid amplification technology (iNAT). Results are available within 15 minutes. A color video displayed on the device’s screen walks users through the testing process. A sample receiver is placed in the machine and warmed for 2 minutes. The specimen swab is placed in the cartridge for just 10 seconds, and then a pipette cartridge is used to transfer the sample into a test base. The lid is closed and the testing cycle begins. You can walk away at this point and return in 15 minutes to see the result on the device’s LCD screen.

The overall sensitivity and specificity of the Alere i is extremely high and on par with results produced by lab-based PCR tests (Table 2).10 In addition, the device requires just hundreds of viral particles versus the thousands required by traditional
Because the test is a "molecular test," it is billed under a unique CPT code—87502—that is reimbursed at a higher rate compared with nonmolecular strep tests that are billed under the code 87804. The cost of the Alere i flu test is about $50, with national payments of about $100 per test. Alere provides the testing device if a minimum number of tests are performed each year.

Roche is marketing its own version of the PCR POC test called the cobas Liat ("lab in a tube") system. A nasopharyngeal specimen is placed into a tube of transport media, which is then transferred into a test cartridge that is inserted into the system, with results available in just 20 minutes. The Liat features a touch screen that directs the user to scan the cartridge and input or scan identifying patient information. Note that the transport media/swab kit needed to perform a test is not included with the Liat cartridges and must be purchased separately (these cost $2 to $5 per kit). The prices of the Roche system and testing cartridges are not yet available. The Roche test is billed under the CPT code 87502, which is reimbursed at $100 per test. As with the Alere device, the results produced by the Liat are comparable to lab-based PCR systems, with a level of detection superior to all the tests discussed here.11 As of this writing, Roche has just been granted approval for its new test that enables users to test a nasopharyngeal sample for influenza A and B as well as RSV simultaneously.

Whenever a new technology is introduced (such as molecular POC tests), insurance reimbursement can be uncertain. Because the cost of molecular tests is higher than lateral flow assays, it is prudent to get pre-authorizations from insurance companies prior to adopting this new technology.

**Stay tuned!**

In anticipation of flu season, you now are informed regarding what technologies will enable you to accurately diagnose influenza and make prudent use of antiviral therapy. I appreciate your thoughts and opinions regarding office technology.

### Table 2

<table>
<thead>
<tr>
<th>TECHNOLOGY</th>
<th>EXAMPLE</th>
<th>SPECIMEN</th>
<th>SENSITIVITY/ SPECIFICITY</th>
<th>TEST TIME</th>
<th>LEVEL OF DETECTION (TCID₅₀/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral flow immunoassay</td>
<td>BinaxNOW Influenza</td>
<td>NP or N</td>
<td>A: 64.6%/99.1% B: 52.2%/99.8%</td>
<td>15 min</td>
<td>~10⁰</td>
</tr>
<tr>
<td>Digital immunoassay</td>
<td>BD Veritor System-Influenza</td>
<td>NP or N</td>
<td>A: 90.2%/99.7% B: 87.5%/100%</td>
<td>10 min</td>
<td>~10⁵</td>
</tr>
<tr>
<td>Fluorescent immunoassay</td>
<td>Sofia Influenza A+B FIA</td>
<td>N, NP, NPA, NPW</td>
<td>A: 94%/95% B: 89%/96%</td>
<td>15 min</td>
<td>~10²</td>
</tr>
<tr>
<td>Isothermal nucleic acid amplification</td>
<td>Alere i Influenza</td>
<td>N</td>
<td>A: 99.3%/98% B: 97.6%/100%</td>
<td>15 min</td>
<td>~10²</td>
</tr>
<tr>
<td>Real-time PCR</td>
<td>Cobas Liat PCR System</td>
<td>NP</td>
<td>A: 97.7%/98.6% B: 98.6%/99.4%</td>
<td>20 min</td>
<td>~10⁻²</td>
</tr>
</tbody>
</table>

Abbreviations: N, nasal swab; NP, nasopharyngeal; NPA, nasopharyngeal aspirate; NPW, nasopharyngeal wash; PCR, polymerase chain reaction; POC, point of care; TCID₅₀/mL, tissue culture infectious dose (dose of virus that will produce pathological change in 50% of cell cultures inoculated).
Some uropathogens more associated with pyuria than others

A new study demonstrated that in children with an apparent urinary tract infection (UTI), the proportion with pyuria varied significantly depending on the uropathogen associated with the infection.

The study was conducted in 1181 children who had symptoms consistent with a UTI diagnosis, paired urinalysis and urine culture results, and a positive culture.

Pyuria was found in 87% of these children and was absent in 13%.

Children infected with *Enterococcus* or *Klebsiella* species or with *Pseudomonas aeruginosa* were 3 to 5 times less likely to have pyuria than children with *Escherichia coli*. Children with *Enterococcus*, *Klebsiella*, or *P aeruginosa* also were less likely to have a positive leukocyte esterase on dipstick urinalysis. The proportions of children with pyuria were similar in children aged younger than 2 months and in those aged 2 months or older (Shaikh N, et al. *Pediatrics*. 2016;138[1]:e20160087).

The take-home message here is that when you suspect UTI, the urine culture is still the gold standard for diagnosis. Relying entirely on urinalysis may lead you to miss UTI, especially UTI caused by these less common organisms.

—Michael G Burke, MD

also of note

Artificial sweeteners during pregnancy may be related to infants’ overweight. Investigators used a food frequency questionnaire to assess how often 3003 pregnant women drank artificially sweetened or sugar-sweetened beverages during their second or third trimesters. They then analyzed how this data correlated with the body mass index of these mothers’ babies at age 1 year. The infants born to mothers who drank artificially sweetened beverages every day were twice as likely to be overweight at 1 year of age as infants born to mothers who did not drink these beverages. Interestingly, investigators found no comparable associations for sugar-sweetened drinks (Azad MB, et al. *JAMA Pediatr*. 2016;170[7]:662-670).

For references, go to ContemporaryPediatrics.com/opioids-athletics
In 1901, in the then-German city of Breslau situated along the River Odra, skin and venereal disease expert Alfred Blaschko presented his report, *Nerve Distribution in the Skin in Relation to Diseases of the Skin*, to the German Dermatological Society Congress. Blaschko explained to those gathered that the curious lines of distribution seen in certain dermatologic conditions correspond to the developmental pattern of skin cell precursors. This phenomenon is now known as the lines of Blaschko.

**Epidemiology and clinical findings**

Lichen striatus (LS), a common, asymptomatic, self-limited skin disease of unknown etiology that is most commonly found among children aged 5 to 15 years, is just one of many conditions that follow this Blaschkoid pattern.  

Lichen striatus is characterized by flesh-colored to purple erythematous, discrete, and confluent flat-topped papules with fine overlying scale that form a linear unilateral plaque. The best-studied risk factor for LS is atopy, present in 20% to 85% of cases. Xerosis, vitiligo, and pityriasis alba also have been associated with LS.

Lichen striatus manifests on the face in 3% to 15% of cases in children, with some reports stating that it is probably even more common than many estimates suggest. However, the location of LS seems to have little effect on its natural history. Onset is usually sudden, with progression over days or weeks, and spontaneous regression is gradual, within 6 to 24 months. Resolution leaves a transitory residual hypopigmentation that is most prominent in those with a dark complexion, such as this patient.

**Differential diagnosis**

Lichen striatus should be considered in any child with an acquired papular eruption on the face following the lines of Blaschko. Differential diagnosis may include multiple linear papular eruptions, including linear lichen nitidus, linear psoriasis, lichen planus, and blaschkitis, to name a few, yet LS, particularly facial LS, should be considered clinically given that its histologic features are not specific.

**Laboratory findings**

In atypical cases, however, biopsy may be indicated. Histology shows superficial and deep perivascular lymphocytic infiltrate, hyperkeratosis, mild spongiosis with lymphocytic exocytosis, and appendageal involvement.

**Treatment and outcome**

Treatment of facial LS with topical steroids is controversial, and non-steroidal topical therapy has limited supporting data. Therefore, observation of the self-limiting LS was recommended to the patient, accompanied by the administration of sugar-free, organic lollipops.

Mr Simkin is a fourth-year medical student at Johns Hopkins University School of Medicine, Baltimore, Maryland. Dr Oyesanya is a second-year (PGY-3) resident in Dermatology, Johns Hopkins University School of Medicine, Baltimore. Dr Cohen, section editor for Dermcase, is professor of Pediatrics and Dermatology, Johns Hopkins University School of Medicine, Baltimore. The authors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article. Vignettes are based on real cases that have been modified to focus on key teaching points. Images also may be edited or substituted.

**REFERENCES**

Linear papular eruption grows on boy’s neck

DAREN J SIMKIN, BA, MS4; TOLA OYESANYA, MD; BERNARD A COHEN, MD

THE CASE

A father brings his 12-year-old son to the clinic for evaluation of a skin eruption that has been on the back of the boy’s neck for a year, but which just began to extend behind his ear. The rash is asymptomatic, and the otherwise healthy patient is annoyed that he has to spend a beautiful morning in a physician’s office. FOR MORE INFORMATION ABOUT THIS CASE, TURN TO PAGE 55.
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## Look how Children’s Claritin stacks up

<table>
<thead>
<tr>
<th>Children’s Claritin Grape Syrup</th>
<th>Children’s Allegra® Berry Syrup</th>
<th>Children’s ZYRTEC® Grape Syrup</th>
<th>Children’s Benadryl® Cherry Syrup</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Drowsy</strong> (based on label direction)</td>
<td>✓</td>
<td>✓</td>
<td>◯</td>
</tr>
<tr>
<td><strong>24-Hour Once-Daily Dosing</strong></td>
<td>✓</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td><strong>Indicated for Kids Ages 2+</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>#1 Pediatrician-Recommended Non-Drowsy OTC Oral Allergy Brand¹</strong></td>
<td>✓</td>
<td>◯</td>
<td>◯</td>
</tr>
</tbody>
</table>

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¹ Data on file. Bayer.