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PERSONALIZED DOsing FOR YOUR PATIENTS WITH ADHD

The Tris Pharma family of products may help your patients 6 years and older with Attention Deficit Hyperactivity Disorder (ADHD)

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TRIS PHARMA: BRINGING INNOVATION THROUGH LIQUIXR® TECHNOLOGY

› Ion exchange polymer chemistry enables continuous release of the medication throughout the day
› Suspension formulations allow for dose titration in smaller increments

INDICATION
DYANAVEL XR (amphetamine), Quillivant XR (methylphenidate HCl), and QuilliChew ER (methylphenidate HCl) are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE
CNS stimulants, including DYANAVEL XR, Quillivant XR, QuilliChew ER, and other amphetamine-containing or methylphenidate-containing products, 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, Quillivant XR, and QuilliChew ER are contraindicated:
  • in patients known to be hypersensitive to amphetamine, methylphenidate, or other components of DYANAVEL XR, Quillivant XR, and QuilliChew ER. Hypersensitivity reactions, such as angioedema and anaphylactic reactions, have been reported.
  • in patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs, because of risk of hypertensive crisis.

• Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, and other serious cardiac problems. Sudden death, stroke, and myocardial infarction have been reported in adults treated with CNS stimulants at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious cardiac problems when taking CNS stimulants at recommended doses for ADHD. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with DYANAVEL XR, Quillivant XR, and QuilliChew ER.

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

• CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. They may induce a mixed/manic episode in patients with bipolar disorder. Assess for presence of bipolar disorder prior to initiating treatment. At recommended doses, stimulants may cause psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania, in patients without prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing DYANAVEL XR, Quillivant XR, or QuilliChew ER.

Please see Brief Summary of Prescribing Information for DYANAVEL XR, Quillivant XR, and QuilliChew ER, including Boxed Warning regarding Abuse and Dependence, on following pages.
For patients 6 years and older with ADHD, choose the Tris Pharma family of products

**METHYLPHENIDATE**

For your newly diagnosed patients

- **Quillivant XR**
  - For extended-release oral suspension
  - Microtitration in as little as 2 mL to 4 mL
  - Starting dose: 20 mg (4 mL) once daily, with a maximum daily dose of 60 mg (12 mL)
    - Adjust dose in 10-mg (2 mL) to 20-mg (4 mL) increments weekly
    - After reconstitution by the pharmacist, 5 mL of Quillivant XR = 25 mg of methylphenidate HCl

For dosing flexibility in a tablet

- **QuilliChew ER**
  - Microtitration in as little as 1 mL to 2 mL
  - Starting dose: 20 mg once daily, with a maximum daily dose of 60 mg
    - Adjust dose in 10-mg, 15-mg, or 20-mg increments weekly
    - Available in 20-mg, 30-mg, and 40-mg tablets; 20-mg and 30-mg tablets are scored to allow dose titration

**AMPHETAMINE**

For patients ready for their first amphetamine

- **Dyanavel XR**
  - Microtitration in as little as 1 mL to 2 mL
  - Starting dose: 2.5 mg (1 mL) or 5 mg (2 mL) once daily, with a maximum daily dose of 20 mg (8 mL)
    - Adjust dose in 2.5-mg (1 mL) to 10-mg (4 mL) increments every 4 to 7 days
    - 1 mL of DYANAVEL XR = 2.5 mg of amphetamine base

**ADDITIONAL DOSING INFORMATION**

- Medication should be dosed orally, once daily in the morning, with or without food. Titrate dose until optimal response or maximum dose is achieved.
- If switching from other methylphenidates to Quillivant XR/QuilliChew ER, or, from other amphetamines to DYANAVEL XR, discontinue that treatment, then titrate with Quillivant XR/QuilliChew ER or DYANAVEL XR. Do not substitute for other methylphenidates or amphetamines on a milligram-per-milligram basis, because of different methylphenidate or amphetamine base compositions and differing pharmacokinetic profiles.
- Prior to treatment, assess for the presence of cardiac disease and risk of abuse. Maintain careful prescription records, educate patients about abuse, and monitor for signs of abuse and overdose. Periodically re-evaluate the need for medication use and reduce dosage or discontinue treatment.
- There are no data on the effectiveness or safety in patients switched from any one of the above treatments to another.

Eligible patients may pay as little as $20 per prescription. Terms and conditions apply.

**IMPORTANT SAFETY INFORMATION (cont’d)**

- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients with ADHD; monitor weight and height during treatment with DYANAVEL XR, Quillivant XR, and QuilliChew ER. Treatment may need to be interrupted in children not growing or gaining weight as expected.
- CNS stimulants 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.

Please see additional Important Safety Information on the following page.
IMPORTANT SAFETY INFORMATION (cont’d)

- Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed.
- Serotonin syndrome risk is increased when DYANAVEL XR is co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), MAOIs, and during overdosage situations. If it occurs, discontinue DYANAVEL XR and any concomitant serotonergic agents immediately, and initiate supportive treatment.
- QuilliChew ER contains phenylalanine, a component of aspartame, and can be harmful to patients with phenylketonuria (PKU).
- Most common adverse reactions observed with amphetamine products: dry mouth, anorexia, weight loss, abdominal pain, nausea, insomnia, restlessness, emotional lability, dizziness, and tachycardia.
- Based on limited experience with DYANAVEL XR in controlled trials, 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 to 12 years) were: epistaxis (DYANAVEL XR 4%, placebo 0%), allergic rhinitis (4%, 0%) and upper abdominal pain (4%, 2%).
- Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) adverse reactions are: appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, blood pressure increased.
- There is limited experience with Quillivant XR and QuilliChew ER in controlled trials.
  - Quillivant XR: The most common (≥2% in the Quillivant XR group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 45 ADHD patients (ages 6 to 12 years) in Quillivant XR compared to placebo were affect lability (9% Quillivant XR, 2% placebo), excoriation (4%, 0%), initial insomnia (2%, 0%), tic (2%, 0%), decreased appetite (2%, 0%), vomiting (2%, 0%), motion sickness (2%, 0%), eye pain (2%, 0%), and rash (2%, 0%).
  - QuilliChew ER: The most common (≥2% in the QuilliChew ER group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 90 pediatric subjects (ages 6 to 12 years) in QuilliChew ER compared to placebo were decreased appetite (2.4%, 0%), headache (2.4%, 0%), and weight decreased (2.4%, 0%).
- DYANAVEL XR, Quillivant XR, and QuilliChew ER use during pregnancy may cause fetal harm.
- Breastfeeding is not recommended during treatment with DYANAVEL XR, Quillivant XR, or QuilliChew ER.

Please see Brief Summary of Prescribing Information for DYANAVEL XR, Quillivant XR, and QuilliChew ER, below and on following pages.
in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

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

Priapism: Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Serotonin Syndrome: Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonergic neurotransmitter systems such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tryptophan, atypical antipsychotics, fentanyl, lithium, trazodone, and St. John’s Wort. Amphetamines and amphetamine derivatives are known to be metabolized, to some degree, by cytochrome P450 2D6 (CYP2D6). The potential for a pharmacokinetic interaction exists with the co-administration of CYP2D6 inhibitors which may increase the risk of serotonin syndrome with increased exposure to Dyanavel XR. In these situations, consider a non-therapeutic serotonin drug or an alternative drug that does not inhibit CYP2D6. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Concomitant use of Dyanavel XR with MAOIs is contraindicated. Discontinue treatment with Dyanavel XR and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur, and initiate supportive symptomatic treatment. If concomitant use of Dyanavel XR with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate Dyanavel XR with lower doses, monitor patients for the emergence of serotonin syndrome during drug initiation or titration, and inform patients of the increased risk for serotonin syndrome.

Risks in Patients with Phenylketonuria: Phenylalanine can be harmful to patients with phenylketonuria (PKU). QuilliCheer ER extended-release chewable tablets contain phenylalanine, a component of aspartame. Each 20 mg, 30 mg, and 40 mg extended-release chewable tablet contains 5 mg, 4.5 mg, and 6 mg phenylalanine, respectively. Before prescribing QuilliCheer ER in patients with PKU, consider the combined daily amount of phenylalanine from all sources, including QuilliCheer ER.

ADVERSE REACTIONS

Clinical Trial Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Clinical Trials Experience with Other Amphetamine Products in Pediatric Patients and Adults with ADHD Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, irritability, euphoria, dyskinesia, dysphoria, depression, tremor, tics, aggression, anger, logorrhea. Eye Disorders: Vision blurred, mydriasis. Gastrointestinal: Diarrhea, dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and 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 necrosis have been reported. Endocrine: Impotence, changes in libido. Skin: Alopecia. Clinical Trials Experience with Dyanavel XR in Pediatric Patients with ADHD: 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. Adverse reactions occurring in ≥2% of subjects in the Dyanavel XR group (N=52) and greater than that in the placebo group (N=48) during the double blind phase of the Phase 3 controlled study in patients with ADHD aged 6 to 12 years were: epistaxis (Dyanavel XR 3.8%, Placebo 0%), allergic rhinitis (3.8%, 0%) and upper abdominal pain (3.8%, 0%). Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, weight decreased, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, tremor, dry mouth, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia. Clinical Trials Experience with QuilliCheer ER in Children and Adolescents with ADHD: There is limited experience with QuilliCheer ER in controlled trials. Based on this limited experience, the adverse reaction profile of QuilliCheer XR appears similar to other methylphenidate extended-release products. Adverse reactions reported in ≥2% in the QuilliCheer XR group and greater than placebo in the controlled cross-over phase of the Phase 3 study conducted in 46 ADHD patients ages 6 to 12 years were: affect lability (QuilliCheer XR 9%, Placebo 2%), excitement (4%, 0%), appetite decreased (2%, 0%), initial insomnia (2%, 0%), tic (2%, 0%), decreased appetite (2%, 0%), vomiting (2%, 0%), motion sickness (2%, 0%), eye pain (2%, 0%), rash (2%, 0%). Clinical Trials Experience with QuilliCheer ER in Children with ADHD: There is limited experience with QuilliCheer ER in controlled trials. The safety data in this section is based on data from a laboratory classroom study conducted in 90 pediatric subjects (ages 6 to 12 years) with ADHD. Adverse reactions reported in ≥2% in the QuilliCheer XR group (N=42) and greater than placebo (N=44) in the double-blind, randomized, placebo-controlled parallel group study with Dyanavel XR were: decreased appetite (2.4%, Placebo 0%), aggression (2.4%, 0%), emotional poverty (2.4%, 0%), nausea (2.4%, 0%), headache (2.4%, 0%), weight decreased (2.4%, 0%). Postmarketing Experience: The following adverse reactions have been identified during post-approval use of other amphetamine and methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Amphetamine products Allergic: urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens-Johnson Syndrome and toxic epidermal necrosis have been reported. Cardiovascular: palpitations, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. Central Nervous System: restlessness, irritability, euphoria, dyskinesia, dysphoria, depression, tremor, aggression, anger, logorrhea, and paraphrenia (including formulation). Endocrine: impotence, changes in libido, frequent or prolonged erections. Eye Disorders: vision blurred, mydriasis. Gastrointestinal: unpleasant taste, constipation, other gastrointestinal disturbances. Musculoskeletal, Connective Tissue, and Bone Disorders: rhabdomyolysis. Psychiatric Disorders: dermatillomaniia, bruxism. Skin: alopecia. Vascular Disorders: Raynoud’s phenomenon. Methylphenidate products Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura. Cardiovascular Disorders: Angina pectoris, Bradycardia, Extrastyle, Supraventricular tachycardia, Ventricular Extrastyle. Eye Disorders: Diplopia, Mydriasis, Visual impairment. General Disorders: Chest pain, Chest discomfort, Hypertrophia. Hepatobiliary Disorders: Severe hepatitis. Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Blisters conditions, Eosinophilic conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC. Investigations: Alkaline phosphatase increased, Bilirubin increased. Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal. Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis. Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs. Psychiatric Disorders: Disorientation, Hallucinations, hallucination auditory, Hallucination visual, Libido changes, Mania, Urogenital System: Priapism. Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema. Vascular Disorders: Raynoud’s phenomenon.

DRUG INTERACTIONS

Clinically Important Drug Interactions Monoamine Oxidase Inhibitors (MAOIs): Do not administer the Dyanavel XR, Quillivant XR, or QuilliCheer ER concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure. Examples: Selegiline, tranylcypromine, isocarboxazid, phenelzine,lineozil, methylene blue. Serotonergic Drugs: The concomitant use of Dyanavel XR and serotonergic drugs increases the risk of serotonin syndrome. Initiate with lower doses and monitor patients for signs and
symptoms of serotonin syndrome, particularly during Dyanavel XR initiation or dosage increase. If serotonin syndrome occurs, discontinue Dyanavel XR and the concomitant serotonin drug(s). Examples: Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John’s Wort. CYP2D6 Inhibitors: The concomitant use of Dyanavel XR and CYP2D6 inhibitors may increase the exposure of Dyanavel XR compared to the use of Dyanavel XR alone, and increase the risk of serotonin syndrome. Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during Dyanavel XR initiation and after a dosage increase. If serotonin syndrome occurs, discontinue Dyanavel XR and the CYP2D6 inhibitor. Examples: Paroxetine and fluoxetine (also serotonin drugs), quinidine, ritonavir. Alkalizing Agents: Increase blood levels and potentiate the action of amphetamine. Co-administration of Dyanavel XR and gastrointestinal alkalizing agents should be avoided. Examples: Gastrointestinal alkalizing agents (e.g., sodium bicarbonate); urinary alkalizing agents (e.g. acetazolamide, some thiuramides). Avoid the use of Amphetamines during pregnancy. Lower blood pressure and efficacy of amphetamines. Increase dose based on clinical response. Examples: Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid); urinary acidifying agents (e.g. ammonium chloride, sodium acid phosphate, methenamine salts). Tricyclic Antidepressants: May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated. Monitor frequently and adjust or use alternative therapy based on clinical response. Examples: Desipramine, protriptyline. Drug/Laboratory Test Interactions Amphetamines can cause a significant elevation in plasma cortisol/corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

USE IN SPECIFIC POPULATIONS Pregnancy Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Dyanavel XR during pregnancy. Healthcare providers are encouraged to report all cases to the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or pregnancy.org. The registry is a voluntary, non-identifiable registry used to determine a drug-associated risk of major congenital malformations or miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines. There are limited published studies and small case series that report on the use of amphetamines in pregnant women; however, the data are insufficient to inform any drug-associated risks. Clinical Considerations: Fetal/Neonatal adverse reactions: Amphetamines, such as Dyanavel XR, may cause vasoconstriction, including vasoconstriction of placental blood vessels, and may increase the risk for intrauterine growth restriction. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers. Monitor infants born to mothers taking amphetamines for symptoms of withdrawal, such as feeding difficulties, irritability, agitation, and excessive drowsiness. CNS stimulant medications, such as Dyanavel XR and QuilliChew ER, can cause hypertension and tachycardia, decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy. lactation Risk Summary Based on limited case reports in published literature, amphetamine (d- or d, l-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant and no effects on milk production. However, long term neurodevelopmental effects on infants from stimulant exposure are unknown. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with Dyanavel XR. Limited published literature reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for QuilliChew ER and Quillivant XR, and any potential adverse effects on the breastfed infant from Quillivant XR and QuilliChew ER, or from the underlying maternal condition. Clinical Considerations Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain. Pediatric Use: Safety and effectiveness for Dyanavel XR, Quillivant XR, and QuilliChew ER have been established in pediatric patients with ADHD ages 6 to 17 years. Safety and efficacy of these products in pediatric patients younger than 6 years with ADHD have not been established. Long-Term Growth Suppression Growth should be monitored during treatment with stimulants, including Dyanavel XR, Quillivant XR, and QuilliChew ER. Changes in mean height and weight are not observed in children treated with stimulants. The long-term efficacy of methylphenidate in pediatric patients has not been established. Geriatric Use: Dyanavel XR, Quillivant XR, and QuilliChew ER have not been studied in patients over the age of 65 years.

DRUG ABUSE AND DEPENDENCE Controlled Substance: Dyanavel XR contains amphetamine, and Quillivant XR and QuilliChew ER contain methylphenidate; amphetamine and methylphenidate are Schedule II controlled substances in the U.S. Controlled Substance Act (CSA). Abuse: CNS stimulants including Dyanavel XR, Quillivant XR, and QuilliChew ER, other amphetamines and methylphenidates have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving. Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may use other unapproved routes of administration which can result in overdose and death. To reduce the abuse of CNS stimulants, including Dyanavel XR, Quillivant XR, and QuilliChew ER, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for Dyanavel XR, Quillivant XR, and QuilliChew ER use. Dependence: To reduce the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for Dyanavel XR, Quillivant XR, and QuilliChew ER use. Dependence: Physical dependence (which is manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) can occur in patients treated with CNS stimulants including Dyanavel XR, Quillivant XR, and QuilliChew ER. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; fatigue; vivid, unpleasant dreams; insomnia or hypersonia; increased appetite; and psychomotor retardation or agitation.

OVERDOSAGE Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdose with amphetamine or methylphenidate. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses. Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma. Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis. Manufactured by: Tris Pharma, Inc., Monmouth Junction, NJ 08852 www.TrisPharma.com

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95% CURE RATE AGAINST PINWORM¹

- EMVERM contains mebendazole, the active ingredient that has been prescribed by physicians for more than 40 years²
- The AAP Red Book recommends mebendazole as one of the drugs of choice for pinworm infections³
- The CDC recommends treating the entire household where more than one member is infected or where repeated, symptomatic infections occur⁴
- Patients should be prescribed 2 tablets. EMVERM can often cure pinworm infection with a single tablet. However, a second tablet may be necessary after 3 weeks to prevent reinfection and to kill any worms that hatch after the first treatment⁴:
  - One 100 mg tablet is the same dose for adults and children⁵
  - Chewable, kid-friendly tablet can also be swallowed whole or crushed and mixed with food⁶

ELIGIBLE PATIENTS MAY PAY AS LITTLE AS $5.⁷
LEARN MORE AT EMVERMSAVINGS.COM/CP

Subject to eligibility. Individual out-of-pocket costs may vary. Not valid for patients covered under Medicare, Medicaid, or other federal or state program. Please see full terms, conditions, and eligibility criteria at EmvermSavings.com.
AAP, American Academy of Pediatrics.

INDICATION
EMVERM is indicated for the treatment of patients two years of age and older with gastrointestinal infections caused by Ancylostoma duodenale (hookworm), Ascaris lumbricoides (roundworm), Enterobius vermicularis (pinworm), Necator americanus (hookworm), and Trichuris trichiura (whipworm).

IMPORTANT SAFETY INFORMATION
Contraindication: EMVERM is contraindicated in persons with a known hypersensitivity to the drug or its excipients (mebendazole, microcrystalline cellulose, corn starch, anhydrous lactose, sodium starch glycolate, magnesium stearate, stearic acid, sodium lauryl sulfate, sodium saccharin, and FD&C Yellow No. 6).

Warnings and Precautions:
- Risk of convulsions: Convulsions in infants below the age of 1 year have been reported.
- Hematologic effects: Neutropenia and agranulocytosis have been reported in patients receiving mebendazole at higher doses and for prolonged duration. Monitor blood counts in these patients.
- Metronidazole and serious skin reactions: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) have been reported with the concomitant use of mebendazole and metronidazole.

Adverse Reactions from Clinical Trials: Anorexia, abdominal pain, diarrhea, flatulence, nausea, vomiting, rash.

Adverse Reactions from Postmarketing Experience with Mebendazole: Agranulocytosis, neutropenia, hypersensitivity including anaphylactic reactions, convulsions, dizziness, hepatitis, abnormal liver tests, glomerulonephritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, exanthema, angioedema, urticaria, alopecia.

*Includes mebendazole formulations, dosages and treatment: duration other than EMVERM 100 mg chewable tablet.

Drug Interactions: Concomitant use of EMVERM and metronidazole should be avoided.

Use in Specific Populations:
- Pregnancy: Mebendazole use in pregnant women has not reported a clear association between mebendazole and a potential risk of major birth defects or miscarriages. However, there are risks to the mother and fetus associated with untreated helminth infection during pregnancy.
- Lactation: Limited data from case reports demonstrate that a small amount of mebendazole is present in human milk following oral administration. There are no reports of effects on the breastfed infant.
- Pediatric Use: The safety and effectiveness of EMVERM 100 mg chewable tablet has not been established in pediatric patients less than two years of age.
- Geriatric Use: Clinical studies of mebendazole did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

Overdosage: In patients treated at dosages substantially higher than recommended or for prolonged periods of time, the following adverse reactions have been reported: alopecia, reversible transaminase elevations, hepatitis, agranulocytosis, neutropenia, and glomerulonephritis.
- Symptoms and signs of overdose: In the event of accidental overdose, gastrointestinal signs/symptoms may occur.
- Treatment of overdose: There is no specific antidote.

Patient Counseling: Healthcare professionals should advise the patient to read the FDA-approved patient labeling (Patient Information). Advise patients that:
- Taking EMVERM and metronidazole together may cause serious skin reactions and should be avoided.
- EMVERM can be taken with or without food.

To report SUSPECTED ADVERSE REACTIONS contact Amneal Specialty, a division of Amneal Pharmaceuticals LLC at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Full Prescribing Information at www.EMVERMHCP.com and Brief Summary on following pages.
**EMVERM** (mebendazole) 100 mg Chewable Tablets

**BRIEF SUMMARY:** Complete information about EMVERM® can be found in the Full Prescribing Information.

**INDICATIONS AND USAGE**
EMVERM® is indicated for the treatment of patients two years of age and older with gastrointestinal infections caused by *Ancylostoma duodenale* (hookworm), *Ascaris lumbricoides* (roundworm), *Enterobius vermicularis* (pinworm), *Necator americanus* (hookworm), and *Trichuris trichiura* (whipworm).

**DOSE AND ADMINISTRATION**
The recommended dosage for EMVERM® is described in Table 1 below. The same dosage schedule applies to adults and pediatric patients two years of age and older. The tablet may be chewed, swallowed, or crushed and mixed with food.

**Table 1: Dosage of EMVERM in Adult and Pediatric Patients (two years of age and older)**

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

**CONTRAINDICATIONS**
EMVERM® is contraindicated in persons with a known hypersensitivity to the drug or its excipients (mebendazole, microcrystalline cellulose, corn starch, anhydrous lactose, sodium starch glycolate, magnesium stearate, stearic acid, sodium lauryl sulfate, sodium saccharin, and FD&C Yellow #6).

**WARNINGS AND PRECAUTIONS**

**Risk of Convulsions**
Although EMVERM® is approved for use in children two years of age and older, convulsions have been reported in infants below the age of 1 year during post-marketing experience with mebendazole, including EMVERM®.

**Hematologic Effects**
Agranulocytosis and neutropenia have been reported with mebendazole use at higher doses and for more prolonged durations than is recommended for the treatment of soil-transmitted helminth infections. Monitor blood counts if EMVERM® is used at higher doses or for prolonged duration.

**Metronidazole Drug Interaction and Serious Skin Reactions**
Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) have been reported with the concomitant use of mebendazole and metronidazole. Avoid concomitant use of mebendazole, including EMVERM® and metronidazole.

**ADVERSE REACTIONS**

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

The safety of mebendazole was evaluated in 6276 subjects who participated in 39 clinical trials for treatment of single or mixed parasitic infections of the gastrointestinal tract. In these trials, the formulations, dosages and duration of mebendazole treatment varied. Adverse reactions reported in mebendazole-treated subjects from the 39 clinical trials are shown in Table 2.

**Table 2: Adverse Reactions Reported in Mebendazole-treated Subjects from 39 Clinical Trials**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adverse Reaction(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Agranulocytosis, Neutropenia</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Hypersensitivity including anaphylactic reactions</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Convulsions, Dizziness</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>Hepatitis, Abnormal liver tests</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>TEN, SJS, Exanthema, Angioedema, Urticaria, Alopecia</td>
</tr>
</tbody>
</table>

*Includes mebendazole formulations, dosages and treatment duration other than EMVERM® 100 mg tablet

**Postmarketing Experience**
The following adverse reactions have been identified in adult and pediatric patients postmarketing with mebendazole formulations and dosages other than the EMVERM® 100 mg chewable tablet. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Table 3: Adverse Reactions Identified During Postmarketing Experience with Mebendazole**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adverse Reaction(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Convulsions</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>TEN, SJS, Exanthema, Angioedema, Urticaria, Alopecia</td>
</tr>
</tbody>
</table>

*Includes mebendazole formulations, dosages and treatment duration other than EMVERM® 100 mg chewable tablets

**DRUG INTERACTIONS**
Concomitant use of mebendazole, including EMVERM®, and metronidazole should be avoided.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**
The available published literature on mebendazole use in pregnant women has not reported a clear association between mebendazole and a potential risk of major birth defects or miscarriages [see Data]. There are risks to the mother and fetus associated with untreated helminthic infection during pregnancy [see Clinical Considerations].

In animal reproduction studies, adverse developmental effects (i.e., skeletal malformations, soft tissue malformations, decreased pup weight, embryolethality) were observed when mebendazole was administered to pregnant rats during the period of organogenesis at single oral doses as low as 10 mg/kg (approximately 0.5-fold the total daily maximum recommended human dose [MRHD]). Maternal toxicity was present at the highest of these doses [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

**Clinical Considerations**

**Disease-Associated Maternal and/or Embryo/Fetal Risks**
Untreated soil transmitted helmith infections in pregnancy are associated with adverse outcomes including maternal iron deficiency anemia, low birth weight, neonatal and maternal death.

**Data**

**Human Data**
Several published studies, including prospective pregnancy registries, case-control, retrospective cohort, and randomized controlled studies, have reported no association between mebendazole use and a potential risk of major birth defects or miscarriage. Overall, these studies did not identify a specific
pattern or frequency of major birth defects with mebendazole use. However, these studies cannot definitely establish the absence of any mebendazole-associated risk because of methodological limitations, including recall bias, confounding factors and, in some cases, small sample size or exclusion of first trimester mebendazole exposures.

**Animal Data**

Embryo-fetal developmental toxicity studies in rats revealed no adverse effects on dams or their progeny at doses up to 2.5 mg/kg/day on gestation days 6–15 (the period of organogenesis). Dosing at ≥10 mg/kg/day resulted in a lowered body weight gain and a decreased pregnancy rate. Maternal toxicity, including body weight loss in one animal and maternal death in 11 of 20 animals, was seen at 40 mg/kg/day. At 10 mg/kg/day, increased embryo-fetal resorption (100% were resorbed at 40 mg/kg/day), decreased pup weight and increased incidence of malformations (primarily skeletal) were observed. Mebendazole was also embryotoxic and teratogenic in pregnant rats at single oral doses during organogenesis as low as 10 mg/kg (approximately 0.5-fold the total daily MRHD, based on mg/m²).

In embryo-fetal developmental toxicity studies in mice dosed on gestation days 6–15, doses of 10 mg/kg/day and higher resulted in decreased body weight gain at 10 and 40 mg/kg/day and a higher mortality rate at 40 mg/kg/day. At doses of 10 mg/kg/day (approximately 0.2-fold the total daily MRHD, based on mg/m²) and higher, embryo-fetal resorption increased (100% at 40 mg/kg) and fetal malformations, including skeletal, cranial, and soft tissue anomalies, were present. Dosing of hamsters and rabbits did not result in embryotoxicity or teratogenicity at doses up to 40 mg/kg/day (1.6 to 3.9-fold the total daily MRHD, based on mg/m²).

In a peri- and post-natal study in rats, mebendazole did not adversely affect dams or their progeny at 20 mg/kg/day. At 40 mg/kg (1.9-fold the total daily MRHD, based on mg/m²), a reduction of the number of live pups was observed and there was no survival at weaning. No abnormalities were found on gross and radiographic examination of pups at birth.

**Lactation**

**Risk Summary**

Limited data from case reports demonstrate that a small amount of mebendazole is present in human milk following oral administration. There are no reports of effects on the breastfed infant, and the limited reports on the effects on milk production are inconsistent. The limited clinical data during lactation precludes a clear determination of the risk of EMVERM® to a breastfed infant; therefore, developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for EMVERM® and any potential adverse effects on the breastfed infant from EMVERM® or from the underlying maternal condition.

**Pediatric Use**

The safety and effectiveness of EMVERM® 100 mg chewable tablets has not been established in pediatric patients less than two years of age. Convulsions have been reported with mebendazole use in children less than one year of age.

**Geriatric Use**

Clinical studies of mebendazole did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

**OVERDOSAGE**

In patients treated at dosages substantially higher than recommended or for prolonged periods of time, the following adverse reactions have been reported: alopecia, reversible transaminase elevations, hepatitis, agranulocytosis, neutropenia, and glomerulonephritis.

**Symptoms and signs**

In the event of accidental overdose, gastrointestinal signs/symptoms may occur.

**Treatment**

There is no specific antidote.

---

**CLINICAL STUDIES**

Efficacy rates derived from various studies are shown in Table 4 below:

<table>
<thead>
<tr>
<th></th>
<th>Pinworm (enterobiasis)</th>
<th>Whipworm (trichuriasis)</th>
<th>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>

**PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advise patients that:
- Taking EMVERM® and metronidazole together may cause serious skin reactions and should be avoided.
- EMVERM® can be taken with or without food.

To report SUSPECTED ADVERSE REACTIONS, contact Anmeal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Full Prescribing Information including Patient Information at www.emvermhcp.com.

Distributed By: Anmeal Specialty, a division of Anmeal Pharmaceuticals LLC
Bridgewater, NJ 08807
07/2019 PP-XPI-MEB-US-0012
The American Academy of Pediatrics 2019 National Conference and Exhibition in New Orleans this past October yielded a bounty of new and relevant information for today’s pediatricians. Contemporary Pediatrics was there, and in this issue we share the best of the Conference with our audience.

The highlight of the year in the world of pediatric healthcare is the annual American Academy of Pediatrics (AAP) National Conference and Exhibition, where pediatricians from across the United States and the globe assemble to share successes and address new challenges to the practice of healthcare for children.

Contemporary Pediatrics attended this Conference in New Orleans in October, and in this issue we present the highlights of new research that will aid pediatricians in practice today and going forward. Beginning on page 14, you’ll read about advances in detecting acute flaccid myelitis, treating autism in the medical home, managing uncontrolled asthma, and how global climate change is already affecting children’s health. There is clinical advice to deal with vaccine-hesitant parents and to care for families who have lost a child to sudden unexplained death. On the business side, there is practical advice offering strategies for insurance reimbursement. You’ll find even more articles from the AAP Conference on our website: ContemporaryPediatrics.com.

In addition to our special Conference highlights, this issue presents clinical findings that address infectious disease, pediatric pharmacology, dermatology, mental health, respiratory disorders, and metabolic disorders as part of our continuing coverage of these important therapeutic areas of Pediatrics, as well as popular features including the Puzzler and Dermcase that you look for each month.

This exceptional content addresses your need to keep up-to-date on the latest clinical developments in your field of practice. We research for you what is relevant, synthesize the information into a readable package, and present it to you in a way that fits into your busy schedule. That is the continuing mission of this publication. ■

Mike Hennessy, Sr.
Chairman and Founder,
MJH Life Sciences
A novel, once-daily treatment option for patients with ADHD 6 years and older

**Jornay PM**

methylphenidate HCl extended-release capsules

20mg  40mg  60mg  80mg  100mg

**Now Available**

The first and only ADHD stimulant dosed in the evening

Help your patients wake up ready for the day

When dosed in the evening, the delayed-release and extended-release technology of JORNAY PM enables the drug to be delivered in the early morning—and it lasts throughout the day

Mornings matter. Learn more at JORNAYpm.com and prescribe today.

**Indication and Important Safety Information**

**INDICATION**

JORNAY PM is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

**IMPORTANT SAFETY INFORMATION**

**WARNING: ABUSE AND DEPENDENCE**

CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, 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.

**CONTRAINDICATIONS**

- Known hypersensitivity to methylphenidate or other components of JORNAY PM. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate products.
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days because of the risk of hypertensive crisis.

**WARNINGS AND PRECAUTIONS**

- **Serious Cardiovascular Reactions:** Sudden death, stroke, and myocardial infarction have been reported in adults treated with CNS stimulants at recommended doses. Sudden death has been reported in pediatric patients 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 arrhythmias, coronary artery disease, and other serious cardiac problems.
- **Blood Pressure and Heart Rate Increases:** CNS stimulants may cause an increase in blood pressure and heart rate. Monitor all patients for hypertension and tachycardia.
- **Psychiatric Adverse Reactions:** CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychiatric disorder and may induce a manic or mixed episode in patients with bipolar disorder. In patients with no prior history of psychotic illness or mania, CNS stimulants, at recommended doses, may cause psychotic or manic symptoms.
- **Priapism:** Prolonged and painful erections, sometimes requiring intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism has also appeared during a period of drug withdrawal. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed.
- **Peripheral Vasculopathy, including Raynaud’s Phenomenon:** CNS stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud’s phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants.
- **Long-Term Suppression of Growth:** CNS stimulants have been associated with weight loss and slowing of growth in pediatric patients. Monitor height and weight at appropriate intervals in pediatric patients.

**ADVERSE REACTIONS**

- Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) adverse reactions for pediatric patients and adults are: appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased.
- Additional adverse reactions (≥5% and twice the rate of placebo) in pediatric patients 6 to 12 years treated with JORNAY PM: headache, psychomotor hyperactivity, and mood swings.

**PREGNANCY AND LACTATION**

- CNS stimulant medications, such as JORNAY PM, can cause vasoconstriction and thereby decrease placental perfusion.
- The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for JORNAY PM and any potential adverse effects on the breastfed infant from JORNAY PM or from the underlying maternal condition. Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

Please see additional safety information in the Brief Summary of Prescribing Information for JORNAY PM on adjacent pages.

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JORNAY PM™ (methylphenidate hydrochloride) extended-release capsules, for oral use, CII Rx only

BRIEF SUMMARY: Consult Full Prescribing Information for Complete Product Information

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE
CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, 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
JORNAY PM is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

DOSAGE AND ADMINISTRATION
JORNAY PM should be taken only in the evening. Adjust the timing of administration between 6:30 PM and 9:30 PM to optimize the tolerability and efficacy the next morning and throughout the day.

The recommended starting dose for patients 6 years and above is 20 mg daily in the evening. Dosage may be increased weekly in increments of 20 mg per day up to a maximum daily dose of 100 mg. Capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce. Do not substitute for other methylphenidate products on a milligram-per-milligram basis.

CONTRAINDICATIONS
Hypersensitivity to methylphenidate or other components of JORNAY PM. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate products.

Concomitant treatment with monoamine oxidase inhibitors, or within 14 days following discontinuation of a monoamine oxidase inhibitor, because of the risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS
Potential for Abuse and Dependence CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines have a high potential for abuse and dependence. Assess the risk for abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.

Serious Cardiovascular Reactions
Sudden death, stroke, and myocardial infarction have been reported in adults treated with CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, and other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with JORNAY PM.

Blood Pressure and Heart Rate Increases CNS stimulants may cause an increase in blood pressure (mean increase 2 to 4 mmHg) and heart rate (mean increase 3 to 6 bpm). Individuals may have larger increases. Monitor for hypertension and tachycardia.

Psychiatric Adverse Reactions
Exacerbation of Pre-existing Psychosis CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. Induction of a Manic Episode in stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. Induction of a Manic Episode in stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. Induction of a Manic Episode in stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Long-term Suppression of Growth CNS stimulants have been associated with weight loss and slowing of growth in pediatric patients. Careful follow-up of weight and height in patients ages 7 to 10 years who were randomized to either methylphenidate or placebo over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and placebo-treated patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth (on average, 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period. Closely monitor growth (weight and height) in children treated with CNS stimulants, including JORNAY PM. Patients not growing or gaining height or weight as expected may need their treatment interrupted.

ADVERSE REACTIONS
Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD
Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, weight decreased, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessless, affect liability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia. Clinical Trials Experience with JORNAY PM in Pediatric Patients
Study 1, conducted in pediatric patients 6 to 12 years of age, was comprised of a 6-week open-label dose-optimization phase in which all patients received JORNAY PM (n=125; mean dose 50 mg), followed by a 1-week, double-blind controlled phase in which patients were randomized to continue JORNAY PM (n=65) or switch to placebo (n=54). During the open-label JORNAY PM treatment phase, adverse reactions reported in >5% of patients included: any insomnia (41%), decreased appetite (27%), affect liability (22%), headache (19%), hypertension (17%), upper abdominal pain (9%), nausea or vomiting (9%), increased diastolic blood pressure (8%), tachycardia (7%), and irritability (6%). Three patients discontinued treatment because of affect liability, panic attacks, and agitation and aggression. Because of the trial design (6-week open-label active treatment phase followed by a 1-week, randomized, double-blind, placebo-controlled withdrawal), the adverse reaction rates described in the double-blind phase are lower than expected in clinical practice. No difference occurred in the incidence of adverse reactions between JORNAY PM and placebo during the 1-week, double-blind, placebo-controlled phase. Study 2 was a 3-week, placebo-controlled study of JORNAY PM (n=81; mean dose 52 mg) in pediatric patients 6 to 12 years. Most Common Adverse Reactions (incidence of ≥ 5% and at a rate at least twice placebo): any insomnia, decreased appetite, headache, vomiting, nausea, psychomotor hyperactivity, and affect liability or mood swings. One patient in the JORNAY PM group discontinued from the study due to mood swings. Table 1 provides the incidence of adverse reactions reported in Study 2 (incidence of 2% or more and at least twice placebo) among pediatric patients 6 to 12 years in a 3-week clinical trial.

Table 1: Adverse Reactions Occurring in ≥2% of JORNAY PM-Treated Pediatric Patients and Greater than Placebo in a 3-Week ADHD Study (Study 2)

<table>
<thead>
<tr>
<th>Body Organ System</th>
<th>Adverse Reaction</th>
<th>JORNAY PM (N=81)</th>
<th>Placebo (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>Any insomnia</td>
<td>33%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Initial insomnia</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Middle insomnia</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Terminal insomnia</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Insomnia, not specified</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Affect liability/Mood swings</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>19%</td>
<td>4%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>10%</td>
<td>5%</td>
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<td></td>
<td>Psychomotor hyperactivity</td>
<td>5%</td>
<td>1%</td>
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<tr>
<td>Cardiovascular disorders</td>
<td>Blood pressure diastolic increased</td>
<td>7%</td>
<td>4%</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting</td>
<td>9%</td>
<td>0%</td>
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<td></td>
<td>Nausea</td>
<td>6%</td>
<td>0%</td>
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<tr>
<td>Infections and infestations</td>
<td>Nasopharyngitis</td>
<td>3%</td>
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<td>Pharyngitis streptococcal</td>
<td>3%</td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Contusion</td>
<td>3%</td>
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<td>Musculoskeletal and procedural complications</td>
<td>Back pain</td>
<td>3%</td>
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</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>2%</td>
<td>0%</td>
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</tbody>
</table>
Postmarketing Experience The following adverse reactions have been identified during postapproval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Blood and Lymphatic System Disorders: Panophotopy, Thrombocytopenia, Thrombocytopenic purpura Cardiac Disorders: Angina pectoris, Bradycardia, Extraesystole, Supraventricular tachycardia, Sinus extrasystole, Sinus tachycardia Eye Disorders: Diplopia, Mydriasis, Visual impairment General Disorders: Chest pain, Chest discomfort, Hyperventilation Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Aural swelling, Bullous conditions, Exfoliative conditions, Urticaria, Pruritus, Rashes, Eruptions, and Exanthema Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal, Severe hepatic injury Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Libido changes, Mania Urogenital System: Priapism Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema Vascular Disorders: Raynaud’s phenomenon

DRUG INTERACTIONS MAO Inhibitors Do not administer JORNAY PM concomitantly with MAOIs or within 14 days after discontinuing MAO treatment. Concomitant use of MAO inhibitors and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

USE IN SPECIFIC POPULATIONS Pregnancy Risk Summary Published studies and postmarketing reports on methylphenidate use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes. No teratogenic effects were observed in embryofetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses up to 2 and 9 times the maximum recommended human dose (MRHD) of 100 mg/day given to adolescents on a mg/m2 basis, respectively. However, spina bifida was observed in rabbits at a dose of 31 times the MRHD given to adolescents. A decrease in pup body weight was observed in a pre- and post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses of 3.5 times the MRHD given to adolescents. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 25% of clinically recognized pregnancies.

Clinical Considerations Fetal/Neonatal Adverse Reactions CNS stimulant medications, such as JORNAY PM, can cause vasocostriction and thereby decrease placental perfusion. No fetal or neonatal adverse reactions have been reported with therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers. Data Human Data A limited number of pregnancies have been published in observational studies and postmarketing reports describing methylphenidate use during pregnancy. Due to the small number of methylphenidate-exposed pregnancies with known outcomes, these data cannot definitively establish or exclude any drug-associated risk during pregnancy.

Data in studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 31 times the MRHD of 100 mg/day given to adolescents on a mg/m2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (9 times the MRHD given to adolescents on a mg/m2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (6 times the MRHD given to adolescents on a mg/m2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (6 times the MRHD given to adolescents on a mg/m2 basis).

Lactation Risk Summary Limited published literature, based on breast milk sampling from five mothers, reports that methylphenidate is present in human milk, which resulted in infant dosages of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. However, long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for JORNAY PM and any potential adverse effects on the breastfed infant from JORNAY PM or from the underlying maternal condition. Clinical Considerations Monitor breastfeeding infants for adverse reactions including agitation, insomnia, anorexia, and reduced weight gain.

Pediatric Use The safety and effectiveness of JORNAY PM in pediatric patients less than 6 years have not been established. The safety and effectiveness of JORNAY PM have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled studies in pediatric patients 6 to 12 years, pharmacokinetic data in adults, and safety information from other methylphenidate-containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established. Long-Term Suppression of Growth Growth should be monitored during treatment with stimulants, including JORNAY PM. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted. Juvenile Animal Toxicity Data Rats treated with methylphenidate early in the preweanling period had a decrease in body weight gain, with a 2.5 times the MRHD of 100 mg/day given to children on a mg/m2 basis. Decreased spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 2.5 times the MRHD of 100 mg/day given to children on a mg/m2 basis. In a study conducted prior to pregnancy, when pregnant rats were administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal Day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with ≥ 50 mg/kg/day (approximately ≥ 2.5 times the MRHD of 100 mg/day given to children on a mg/m2 basis), and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (5 times the MRHD of 100 mg/day given to children on a mg/m2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (0.25 times the MRHD of 100 mg/day given to children on a mg/m2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

Geriatric Use JORNAY PM has not been studied in patients older than 65 years of age.

DRUG ABUSE AND DEPENDENCE Controlled Substance JORNAY PM contains methylphenidate, a Schedule II controlled substance.

Abuse CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving. Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. CNS stimulants, including JORNAY PM, may chew, snort, inject, or use other unapproved routes of administration, which can result in overdose and death. To reduce the abuse of CNS stimulants including JORNAY PM, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for JORNAY PM use.

Dependence Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug’s desired and/or undesired effects over time) can occur during chronic therapy with CNS stimulants including JORNAY PM. Dependence Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) can occur in patients treated with CNS stimulants, including JORNAY PM. Withdrawal symptoms after abrupt cessation following prolonged high-dose administration of CNS stimulants include: dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

OVERDOSE Signs and Symptoms Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachyphylaxis, mydriasis, dryness of mucous membranes, and rhabdomyolysis.

Management of Overdose Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice on the management of overdose with methylphenidate. Provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdose with any drug. Consider the possibility of multiple drug overdoses. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.
Acute flaccid myelitis (AFM) is an uncommon but serious condition for which outbreaks have followed a biennial pattern since 2014. With the next surge of AFM cases predicted in 2020, it is important that pediatricians be familiar with its presenting features because early recognition has implications both for the prognosis of the affected child and for enabling research to understand AFM etiology, said Kevin Messacar, MD, at the American Academy of Pediatrics (AAP) 2019 National Conference and Exhibition, October 28, in New Orleans, Louisiana.

Messacar is assistant professor of Pediatrics at the University of Colorado, Denver, a hospitalist, and infectious disease consultant at Children’s Hospital Colorado Anschutz Medical Campus, Aurora. He told attendees that the term AFM was coined in 2014 after groups of children presented with paralysis of the arms, legs, or muscles of the face and throat. In response to reports of these cases, the Centers for Disease Control and Prevention (CDC) established a case definition to both identify cases and quantify their number. According to the CDC, AFM is defined as acute onset of flaccid limb weakness and magnetic resonance imaging (MRI) involvement of predominantly the gray matter of the spinal cord without identified etiology in individuals aged younger than 21 years.

In his session titled “Acute flaccid myelitis,” Messacar presented information on AFM epidemiology, diagnosis, prognosis, and management. He also discussed some recent research advances that are providing insight on infectious causative mechanisms for this recently described disease.

Messacar said that pediatricians should suspect AFM in any child presenting with weakness in the arms or legs, particularly during late summer or early fall, which have been the peak periods for AFM outbreaks. The his-
ory provides another clue to diagnosis as most children will have had a recent febrile illness with respiratory or gastrointestinal symptoms, or signs of hand-foot-mouth disease. The features of the prodromal illness and the prognosis of AFM may vary depending on the associated virus, said Messacar.

The most common virus associated with AFM cases that have occurred throughout the country since 2014 has been enterovirus D68 (EV-D68), but in 2018 in Colorado there was a cluster of cases associated with EV-A71. Most children who had an EV-D68 infection had respiratory symptoms, whereas the initial prodromal illness associated with EV-A71 involved hand, foot, and mouth lesions. In addition, whereas the majority of children with EV-D68–associated AFM have persistent weakness, complete recovery was more common with EV-A71–associated cases.

When AFM is suspected, pediatricians should report cases to their state health department and order an MRI of the brain and spinal cord to confirm the diagnosis. Importantly, they should procure samples as soon as possible from the respiratory tract, blood, stool, and spinal fluid and submit the specimens to the CDC.

“It is hoped that prompt collection of samples from children with AFM will enable identification of its etiology. Unfortunately, the delay between the initial febrile illness and onset of AFM symptoms has been a major impediment to determining the underlying cause,” Messacar said.

“Children typically first experience muscle weakness about 5 to 7 days after the prodromal illness that is likely the inciting infection, and so by the time that AFM is suspected, the window of opportunity to identify a potential pathogen may have passed in some cases,” he said.

Early recognition is also the cornerstone for optimizing management of children with AFM, the mainstay of which is supportive care to maintain breathing, nutrition, and hydration.

“Progressive neurologic injury with AFM can occur quickly, sometimes within a matter of hours, with resulting paralysis of the muscles that support breathing and protect the airway, Messacar pointed out. “Consequently, a significant proportion of children with AFM require intubation and ventilation. Early recognition of AFM is critical so that the necessary support is provided in a timely manner.”

Rehabilitation therapies, including physical therapy, occupational therapy, and speech therapy, should be initiated as soon as the patient is clinically stable and maintained as long as needed to assist children in regaining as much function as possible.

“The majority of children with AFM do not have complete recovery and are left with long-term if not permanent weakness or paralysis. Pediatricians have an important role as quarterback for coordinating ongoing rehabilitation and the complicated care of these children,” Messacar said.

**COMMENTARY**

Acute flaccid myelitis (AFM) has captured national headlines since outbreaks were recognized in the United States in 2014, 2016, and 2018. Similar to poliomyelitis, patients can experience acute onset of flaccid weakness in one or more limbs, and the condition is most common in children.

Whereas the syndrome of flaccid myelitis can be caused by a number of viruses or immune-mediated pathologies, the late-summer outbreaks occurring on alternating years since 2014 are most associated with a specific enterovirus. This has raised a number of scientific questions and public health concerns. With those issues in mind, and because of the current emphasis on early recognition, reporting, and treatment, it is critical for pediatricians to be aware of AFM.

In a session on this topic at the AAP’s 2019 National Conference and Exhibition, Dr. Kevin Messacar discussed a number of important issues. An update on the current epidemiology and clinical presentations of AFM may be particularly valuable for pediatricians considering that early on, the signs of illness may be missed. Reviewing the differential of acute flaccid weakness is critical for pediatricians as patients may rapidly decline neurologically and suffer respiratory difficulties.

Messacar reviewed the data relative to etiology studies, pointing out that the likely cause in the majority of patients is enterovirus D68, which usually causes a mild upper-respiratory syndrome. He noted the prevalence of a prodromal illness in the majority of patients, followed by rapid neurologic...
AAP 2019

decline a week later.

As Dr. Messacar pointed out, early reporting to public health officials and sampling of nasopharyngeal secretions, cerebrospinal fluid, and blood will be critical for CDC-led efforts to confirm the etiology of spinal cord damage. Pediatricians need to be aware of the public health needs and the individual patient needs. Messacar stressed the importance of supportive care, considerations for therapies to limit damage, and the need for early, albeit prolonged, rehabilitation services.

—Benjamin M. Greenberg, MD, MHS, is Distinguished Teaching Professor of Neurology and Pediatrics, University of Texas Southwestern, Dallas, Texas.

AUTISM SPECTRUM DISORDER
What pediatricians should know about diagnosing autism

The pediatric medical home is the perfect place for early diagnosis of children who may have autism spectrum disorder.

CHERYL GUTTMAN KRADER

With autism spectrum disorder (ASD) affecting 1.7% of 8-year-old children, all pediatricians are likely to have many children with ASD under their care.

Pediatricians play an important role in optimizing outcomes for children with ASD, from facilitating early diagnosis, helping families access evidence-based treatments, identifying and treating comorbid medical and behavioral conditions, and serving as a resource to families about the safety and evidence relating to complementary and alternative medical treatments, said Lisa H. Shulman, MD, at the American Academy of Pediatrics (AAP) 2019 National Conference and Exhibition in New Orleans, Louisiana, in October.

In seminar sessions held on Monday, October 28, and Tuesday October 29, Shulman provided an overview of “Autism spectrum disorder: What every pediatrician should know” in 2019.

“Signs of ASD are often apparent by age 18 months or even younger, and yet it remains the case today that the diagnosis is typically not made until after age 4 years. Because of the frequency with which children are seen by their pediatricians when they are very young, the medical home is the perfect place for identifying children who may have ASD,” said Shulman, professor of Pediatrics, Albert Einstein College of Medicine, and interim director of the Rose F. Kennedy Children’s Evaluation and Rehabilitation Center at Montefiore Medical Center, Bronx, New York. “Each encounter over time is an opportunity to not only evaluate developmental milestones but also social functioning.”

Shulman noted the need for following the AAP guidelines on screening for ASD at 18 and 24 months to help improve early identification, and also for pediatricians to not rely solely on completed checklists but to “look with their own eyes” for early signs that are predictive of autism when present at 12 months. These signs include reduced eye contact, failure to respond to name, not pointing to request, and not pointing to show. How easy is it to obtain the child’s attention? To achieve a shared smile in response to a song? How does the child let you know that he/she wants a colorful object out of reach?

A hearing test is essential in the medical workup for a child when ASD is suspected. After hearing is cleared and there is concern about ASD, simultaneous referrals should be made for a diagnostic evaluation and for early intervention to the school district. “The diagnostic evaluation for ASD can take some time. So, do not wait for it to be completed before making the referral to early intervention or the school district,” Shulman said.

She encouraged pediatricians who do not work in a setting with access to an existing ASD diagnostic center to “make a team” of professionals who have an interest and expertise in early ASD diagnosis. The team can be informal and might include a developmental pediatrician, neurologist, or psychiatrist and a psychologist, and/or speech and language pathologist.

Shulman reviewed the Diagnostic and Statistical...
Manual of Mental Disorders (DSM-5) diagnostic criteria and discussed the importance of genetic testing, which over time has led to an increasing number of findings relating to the multiple etiologies of ASD. “There are likely epigenetic or environmental second hits that contribute to the development of ASD in children at biologic risk, and we cannot rule out the possibility that there are unknown risk factors leading to an increase in the incidence of ASD,” she said.

Shulman also covered the evaluation and management of medical and emotional/behavioral issues that are common in children with ASD. “As the primary care provider, pediatricians are ideally positioned to monitor for the various conditions that are often comorbid with ASD, including attention-deficit/hyperactivity disorder, anxiety, restrictive eating habits, and constipation, as well as to give anticipatory guidance regarding relevant safety issues such as elopement,” she said.

With an ever-widening set of complementary and alternative medicine (CAM) interventions being promoted for ASD, and confusion over what is experimental and what is evidence based, Shulman reminded pediatricians to ask families about all the treatments they are accessing for their children.

“If you don’t ask, you may not hear about the various treatments families are utilizing,” she said. “Whereas some CAM treatments are quite safe, others may pose risk such as hyperbaric oxygen, chelation, immunglobulins, stem cell therapies, bleach therapy, and so on. Building on a trusted relationship, pediatricians can be a resource to families to help them sort out safe and effective choices.”

Noting ongoing public concern about vaccination and ASD, Shulman also reviewed the literature on this topic, including the most recent nationwide cohort study that included more than 657,000 children born in Denmark.

“Consistent with previous research, the authors of the Danish study determined that their findings support the conclusion that the measles/mumps/rubella vaccine does not increase the risk for autism or trigger it in susceptible children,” she said.

COMMENTARY

Autism spectrum disorder (ASD) is relevant to every pediatrician given that it affects roughly 2% of children in the United States and has a significant impact on the lives of children and families. Most children are diagnosed after the age of 4, years after evidence-based ASD-specific therapy could have begun.

Pediatricians play a vital role in early identification of children with ASD and with ongoing care throughout childhood and adolescence. It is therefore important that every pediatrician have a sound working knowledge of this condition in order to facilitate early identification, maximize functional outcomes, and support children with ASD and their families.

In a session at the AAP 2019 National Conference and Exhibition, Dr. Lisa Shulman, a developmental pediatrician at Albert Einstein College of Medicine and current member of the AAP Autism Subcommittee, reviewed “What every pediatrician should know” about ASD. She emphasized developmental surveillance, a process in which pediatricians look for early signs of ASD during health supervision visits. Orienting to name and joint attention were identified as social skill milestones that are critical in identifying toddlers at risk for ASD. Screening all children for ASD at the 18- and 24-month visits, as recommended by the AAP, was also viewed as a way to augment developmental surveillance in order to facilitate early identification.

Once a child is identified as at risk, Shulman provided important recommendations for the pediatrician regarding referrals for a comprehensive “team-based” ASD evaluation, along with simultaneous referrals to an early intervention program or to a special education program to get appropriate interventions started. She also reviewed aspects of the medical workup for children with ASD, including genetic testing.

Once the diagnosis is made, Shulman provided important information about identification and management of common co-occurring conditions, addressing questions about integrative, complementary, and alternative medications, and ways to inform parents about the lack of association between vaccines and ASD.

—Paul S. Carbone, MD, is professor of Pediatrics, University of Utah, Salt Lake City, Utah, and chairperson of the AAP Council on Children with Disabilities Autism Subcommittee.
Climate change has adverse effects on children’s health

Children are more physiologically and developmentally vulnerable to health problems created by climate change.

CHERYL GUTTMAN KRADER

The climate crisis is affecting everyone, but no group has more at stake than children. That was the key message of Debra Hendrickson, MD, at the recent American Academy of Pediatrics (AAP) 2019 National Conference and Exhibition in New Orleans, Louisiana. Her talk, “A burning house: Children’s health in the warming world,” addressed conference attendees during the plenary session on Monday, October 28.

Hendrickson told the audience that she was inspired to write a book on the need for action after seeing how climate change was affecting her patients in Reno, Nevada, which in 2016 was named the fastest-warming city in the United States. From infants suffering from wildfire smoke to teenagers anxious about their future in a warming world, children are increasingly feeling the impacts of our changing climate, she said.

Hendrickson urged doctors to better recognize how certain illnesses—such as asthma, allergies, heat illnesses, and infectious diseases carried by ticks and mosquitoes—are being amplified by rising temperatures, more frequent wildfires, hurricanes, flooding, and other climate changes.

“Although the health consequences of climate change are being seen in our patients,” she said, “clinicians may not notice because, much like natural disasters themselves, these diagnoses have always been around but they’re occurring now with greater frequency or severity.”

As part of her talk, Hendrickson told the stories of several children affected by wildfires, hurricanes, or heat waves, and then used their cases to explain why children are more physiologically and developmentally vulnerable to the health problems created by climate change. She emphasized the importance of such storytelling in motivating parents and policymakers to act, arguing that the climate crisis is not just a global crisis, it’s also “a very personal crisis, multiplied many times.”

Hendrickson noted that, ironically, pediatricians today have extraordinary new medications and technology to keep their patients healthy, while at the same time children are facing an existential crisis. “Climate change is threatening everything we work to accomplish for our patients because it is altering the fabric of life itself,” she said.

Far from being a pessimist, Hendrickson emphasized the great potential for pediatricians, as trusted sources of information, to help promote solutions and lead the way, both in their practices and their daily lives. She noted that there are relatively easy steps that each person can take to reduce their own carbon emissions and build a broader movement toward sustainable energy.

For example, most utility companies now offer a “green energy” option that allows customers to choose all-renewable electricity with just a few clicks on their website. Wider adoption of electric cars, which can plug into these all-green homes, and reducing meat and dairy content in our diets would also help, Hendrickson said.

Finally, noting that children are rising up in protest around the world, demanding that governments and corporations act on this issue while there is still time, she called on pediatricians to stand with them.

“We care for the generation that will be most affected by this crisis,” Hendrickson said. “We have a moral obligation to fight for our patients.”

COMMENTARY

Pediatricians are increasingly facing a new issue in child health—climate change. More extreme heat is increasing the risk of heat illness and making it more hazardous for children to play outdoors. Increasing wildfires and rising pollen counts are challenging our ability to protect children’s respiratory health. Warming winters, earlier springs, and higher water temperatures are causing shifts in patterns of some climate-sensitive infectious diseases.

Whereas all people are affected by changing climate conditions, children are among the most vulnerable. It is estimated that children aged younger than 5 years bear greater...
than 80% of the global burden of disease caused by climate change. In recognition of this unique vulnerability, the American Academy of Pediatrics (AAP) was the first major medical society to publish a policy statement on this topic in 2007. The AAP Council on Environmental Health published an updated policy statement and technical report in 2015. These reports identify climate change as one of the greatest threats facing children in the United States and across the world.

Although most pediatricians are seeing affected children today, recognizing the signal of climate change in a busy pediatrician’s office remains challenging. That is because changing patterns in temperature, rainfall, and extreme weather generally amplify and shift conditions pediatricians have always seen, rather than create novel conditions. Noticing changes in seasonal timing, frequency, or severity of common conditions can be a challenge.

In her plenary session at the AAP’s 2019 National Conference, Dr. Debra Hendrickson helped pediatricians to make the connections between changes in the climate and changes in the health of their patients. Through the stories of children affected by extreme heat, weather disasters, and wildfires, she portrayed how changes in climate are affecting the lives of real children in diverse ways across the United States. Many pediatricians are witnessing similar stories but have not yet linked them to environmental change.

Climate change is not only an immediate health threat but is an unprecedented risk to children’s future. As such, it is a moral challenge for all who care for children.

The past year has brought this into focus as children across the world have engaged in school strikes to highlight the urgent need for climate solutions to protect their future. In the United States, children are suing the federal government for its inaction on climate change and the resulting deprivation of their fundamental rights in the case of Juliana v. United States. The AAP signed an amicus brief in support of the children in this case.

Advocacy has been a top priority of the AAP since its inception. The voice of pediatricians has been instrumental in protecting children from a wide range of threats to their health and safety over the century. Dr. Hendrickson discusses the role of pediatricians in speaking out in support of climate solutions. From small changes in our personal lives and practice management, to advocacy in our communities, states, and our nation’s capital, pediatricians can protect every child by working to ensure a safe and healthy planet for their future.

—Samantha Ahdoot, MD, FAAP, is a pediatrician in Alexandria, Virginia, and assistant professor of Pediatrics at Virginia Commonwealth University School of Medicine, Inova

PRACTICE MANAGEMENT

Fight for insurance reimbursement rightfully earned

Understanding which insurance payment denials are valid and which are inappropriate is the first step to practices successfully getting paid for services rendered.

MARY BETH NIERENGARTEN, MA

Pediatricians deserve to be paid appropriately for the services they deliver to patients. The process of documenting what care was delivered, using appropriate International Classification of Diseases (ICD) and Current Procedural Terminology (CPT) codes to submit for billing, adding appropriate modifiers, and successfully transmitting this information through claims processing systems is ripe for problems that can lead to denials. Sometimes denials that are considered “improper” by practices are actually valid denials because the practice made an error or omission in the original claim submission. Other times the claim is inappropriately denied, and practices should be paid for the care delivered.

Understanding which insurance payment denials are valid and which are inappropriate is the first step to successfully getting paid for services rendered. When an inappropriate payment denial is identified, practices need to set up a plan to fight back to ensure compensation for money rightfully earned. This does not require all members of a practice team to be subject matter experts in this area, but a practice should have the collective knowledge to understand and advocate for the financial success of the practice.

In a session delivered on Saturday, October 26, at the
American Academy of Pediatrics (AAP) 2019 National Conference and Exhibition in New Orleans, Louisiana, titled “David and Goliath: How to fight improperly denied insurance claims,” Suzanne Berman, MD, chair of the AAP Section on Administration and Practice Management, and Susan Kressly, MD, chair of the AAP Payer Advocacy Advisory Committee (PAAC), reviewed the billing concepts that all pediatric offices should be familiar with but often aren’t. These include an understanding of ICD specificity and mutually exclusive diagnoses, Medically Unlikely Edit (MUE) and Maximum Frequency per Day (MFD), as well as submission for Multiple Units. The presenters outlined the specific data elements that can often cause a claim to fail and may not even be visible to the pediatrician.

The presenters walked the audience through specific issues important for a practice’s revenue cycle—timely filing, knowing what claims are in which buckets, reviewing denials, submitting corrected claims, the appeals process, and triaging work.

Lastly, the presenters offered a step-by-step approach on how to take on “Goliath” and fight the payer for monies rightfully earned:

- **STEP 1:** Understand the various reasons payers deny claims and what the electronic reason codes defined by the American National Standards Institute (ANSI) mean.
- **STEP 2:** Contact the payer and ask why the claim was denied when the practice believes all the information was appropriately provided in the claim.
- **STEP 3:** Appeal the payer decision.
- **STEP 4:** Effectively advocate with the appropriate information to the appropriate body.

Kressly and Berman emphasized the need to understand the rules governed by the state insurance commissioner as well as state and federal Medicaid agencies to ensure that if an appeal is made it goes to the relevant authority for consideration. The presenters also discussed where pediatricians can go for assistance in both resources and leverage to address payment issues. For AAP members, some of the underutilized member benefits include:

- The AAP coding hotline and various coding resources are available on the AAP website.
- The AAP PAAC creates resources for pediatricians to help them receive appropriate payment from both private payers and Medicaid.
- State chapter Pediatric Councils often have relationships with regional payers and can assist pediatric practices having difficulties getting paid.

“Pediatricians all deserve adequate payment for the services they deliver to the patients of their community,” said Kressly. “Understanding the rules, how to advocate for your practice, and where to look for resources and partners in this work ensures that we have the resources to provide high-quality care to the families of our communities.”

**COMMENTARY**

Understanding the processes that underpin billing and collections is an essential element to running a professional practice of any size. Large healthcare organizations typically have comparably large staffs to effectively manage the “revenue cycle,” which suggests just how important this element of practice management is to the functioning of the clinical. Smaller practices have an equal need to manage billing and collections but don’t typically have the resources to have an equally large staff focused just on this element of practice management.

Drs. Suzanne Berman and Susan Kressly offer a solution in their presentation “David and Goliath: How to fight improperly denied insurance claims”—namely, stay focused on a disciplined approach to the revenue cycle and make full use of the resources offered by organizations such as the AAP to keep up with changes in processes, learn tips for being efficient and effective, and to assist in prioritizing one’s time and effort.

The bottom-line message is that pediatric professionals practicing in all sizes of healthcare organizations can effectively manage their practice’s revenue cycle if they prioritize their efforts and make full use of the shared learnings and resources made available from their colleagues and professional organizations. Even though the payers are a much bigger Goliath than us, we have the benefit of shared experience and a desire to share best practices. This collectively gives us enormous strength to step up to this important task! Go David!

—Angelo P. Giardino, MD, PhD, MPH, is Wilma T. Gibson Presidential Professor, chair, Department of Pediatrics, University of Utah School of Medicine, and chief medical officer, Intermountain Primary Children’s Hospital, Salt Lake City, Utah.
What’s recommended for the 2019 flu shot

The American Academy of Pediatrics has released its recommendations for the upcoming flu season, with this year’s recommendation once again including the live, intranasal vaccine.

RACHAEL ZIMLICH, RN, BSN

The American Academy of Pediatrics (AAP) published its recommendations in Pediatrics,1 and matched the recommendations issued this year by the Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP).2

Flor M. Munoz, MD, MSC, associate professor of Pediatrics and Molecular Virology and Microbiology at Baylor College of Medicine, and medical director for the transplant infectious diseases program at Texas Children’s Hospital in Houston, helped draft the new recommendations and says this is the first year since the live vaccine was reinstated that the AAP and the CDC’s recommendations match. Last year, the CDC offered the live, intranasal version of the influenza vaccine as an option for children, but the AAP held back its recommendation in favor of a longer surveillance period.

“The difference this year is that the AAP and the CDC’s recommendations match, meaning that they both agree that either the injectable or intranasal influenza vaccine can be used,” Munoz says. “There is not a strong argument to recommend one over the other.”

The ACIP made a preferential recommendation for the intranasal vaccine, FluMist, in 2014 for children aged 2 to 8 years because it appeared to offer better protection. The recommendation was reversed in 2015 over concerns about the vaccine’s efficacy against the 2009 H1N1 strain of influenza. The ACIP reinstated its recommendation for FluMist in 2018, after the vaccine manufacturer was able to demonstrate improved efficacy. The AAP, however, withheld its recommendation in favor of reinstating FluMist, noting that it would prefer to observe the new formulation’s efficacy for a longer period of time before making a decision.

Munoz says the AAP’s decision to recommend FluMist is the result of better data showing similar efficacy results between the intranasal and injectable influenza flu vaccines. She notes that protection against H3N2 wasn’t great in either formulation of the vaccine, but both were effective against H1N1.

“This year we do anticipate the majority of the vaccines used will be injectables,” Munoz says, adding that children aged younger than 2 years cannot receive the live, intranasal vaccine.

Munoz also notes that all pediatric influenza vaccines recommended this year are quadrivalent. This has been an ongoing transition from trivalent formulations, she says. As far as which strains the vaccine will cover, this year’s composition of the flu vaccines has been updated to include the influenza A (H1N1) pdm09 and A (H3N2) components. Coverage for B strains is unchanged from previous seasons, according to the AAP.
Impact of the varicella vaccine

The varicella vaccine may have reduced the incidence of herpes zoster. A recent study confirms what others had previously reported.

MIRANDA HESTER, EDITOR

According to the study published in Pediatrics, researchers used children aged 0 to 17 years from 2003 to 2014. They identified cases of herpes zoster using electronic medical records and looking for International Classification of Diseases, Ninth Revision diagnosis code 053. Researchers calculated the incidence rate of herpes zoster per 100,000 person years of health plan membership for all children and also among children who had been vaccinated versus those who had not been. Among children who had been vaccinated, they compared herpes zoster rates by month and year of age at vaccination. The study included 6,372,067 children with 1 month or more of health plan membership. Over the 12-year period, the herpes zoster incidence rate for all children was 74 per 100,000 person years. The rate among children who had been vaccinated for varicella was 38 per 100,000 person years, which was 78% lower than among children who were not vaccinated (170 per 100,00 person years). The incidence of herpes zoster declined by 72% during the study period and the annual rates were consistently lower in children who had been vaccinated than in children who had not been vaccinated.

The researchers say their study confirms the significant decline in herpes zoster incidence among children vaccinated for varicella and highlights the importance of routine varicella vaccination.

For reference, go to ContemporaryPediatrics.com/2019-2020-influenza
Recommendations for prescribing SSRIs

Before turning to selective serotonin reuptake inhibitors (SSRIs) to treat anxiety and depressive disorders in children, check out the freely accessible, genotype-based, drug-dosing online knoweldgesbases for guidance.

MASOUD SALEHI, MD; HASTI HADIZADEH, MD; AUDREY CHANG, BA; MARCO A GRADOS, MD, MPH

Selective serotonin reuptake inhibitors (SSRIs) are a first-line pharmacologic intervention for major depressive and anxiety disorders, but also are indicated for obsessive-compulsive disorder (OCD), premenstrual dysphoric disorder, and bulimia nervosa, among other psychiatric conditions. Due to their relatively low adverse-effect profile—with the exception of a very low rate of self-injurious thoughts and behaviors—and the high prevalence of anxiety and depressive disorders in youth, a significant proportion of SSRIs are prescribed by pediatricians.

The mechanism of action of SSRIs consists of inhibiting the function of the transmembrane presynaptic serotonin transporter (SERT), which in turn increases the availability of serotonin to a myriad of postsynaptic serotonin receptors. Depending on the SSRIL the norepinephrine transporter (NET) and dopamine transporter (DAT) are also weakly inhibited.1 The ensuing serotonergic transmission cascade is still only poorly understood. In particular, neuroplasticity effects may be key in the therapeutic action of SSRIs.2

Pharmacogenomic data available to guide use of SSRIs is cataloged by the Clinical Pharmacogenomics Implementation Consortium (CPIC), with a guideline published in 2015 for CYP2D6 and CYP2C19 polymorphisms.3 Pharmacogenomic data can theoretically be used to personalize biologic information to guide clinicians in choosing among SSRIs to optimize response and decrease adverse effects. However, the data available is only emergent, and should be considered cautiously in its interpretation. In particular, the US Food and Drug Administration (FDA) has not approved pharmacogenomic tests for use in differentiating psychotropic drug choices.

Notwithstanding, CPIC data focuses on polymorphisms in the cytochrome P450 system, which metabolize SSRIs. These polymorphic alleles have been cataloged and may guide treatment, specifically in identifying patients who are refractory to SSRIs or have excessive adverse effects. This article reviews the 2015 CPIC guidelines for 2 CYP450 enzymes, CYP2D6 and CYP2C19, with the addition of recent data available since 2015.4 Of note, the 2015 CPIC guidelines caution using the information provided wholesale to children as most studies have only been performed in adults, with the caveat that cytochrome P450 system activity is generally fully mature by early childhood.

The CYP2D6 gene is highly polymorphic, with over 100 known allele variants and subvariants, which are not straightforward to
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Due to their relatively low adverse-effect profile and the high prevalence of anxiety and depressive disorders in youth, a significant proportion of SSRIs are prescribed by pediatricians.

They vary by race. Given the highly complex nature of the allelic data, therefore, only preliminary guidelines can be provided today even with the best efforts, and it is expected that pharmacogenomic research will clarify these uncertainties in the next decade. The reader is referred to the CPIC 2015 report for full details.

In current practice, given a genetic data readout, the most common alleles expected for CYP2D6 are *1, *2 (both normal function); *6, *9, *10, *41 (all decreased function); and *3, *4, *5, *6 (no function). The CYP2D6 enzyme is the main metabolic agent for fluoxetine (Prozac), and partially for sertraline (Zoloft). Also, CYP2C19 is a polymorphic gene with over 30 known allele variants and subvariants that determine enzyme activity levels, in similar fashion to CYP2D6. The main alleles present in the population for CYP2C19 are *1 (functional), *2 (nonfunctional), and *17 (suprafunctional). In addition, CYP2C19 metabolizes cilostamide (Celexa), escitalopram (Lexapro), and partially sertraline (Zoloft) into less pharmacologically active compounds.

Given that rare variants, and other less well-characterized alleles, are not in current databases, “negative” (normal) reports should be taken with caution. The CPIC suggests that CYP2D6 UM patients forego the use of fluoxetine for another SSRI that relies less on CYP2D6, while CYP2D6 PM patients lower the doses ing to 30% to 50% for fluoxetine and observe closely for adverse effects. Similarly, for CYP2C19 UM patients, higher doses of escitalopram or citalopram will only produce low plasma levels and possible lack of efficacy, with a similar but lesser effect for sertraline. For CYP2C19 PM, the risk of cardiac arrhythmias is posed at higher doses of escitalopram or citalopram, which already may warrant clinical electrocardiographic (ECG) monitoring anyway. A similar consideration is present for sertraline, with usual doses possibly inducing an excess of adverse effects.

Although CPIC guidelines can assist in problematic cases of nonresponse and toxicity, standard pediatric SSRI prescribing practice follows the algorithm of initiating SSRIs at a low dose and increasing gradually to recommended doses until response or adverse effects are encountered. It is interesting to note that in one study pediatricians were more likely to prescribe SSRIs for childhood depression but less for childhood anxiety, despite effect sizes for SSRIs in anxiety disorders being much larger in controlled trials.

Only select studies have examined the use of CYP450 genetic data to guide SSRI treatment since 2015. Bishop and colleagues examined clinical outcomes based on CYP2C19 variants in a cohort of children and adults with autism spectrum disorder (ASD). Eighty-four participants with ASD aged 4 to 45 years com-
completed a 6-week open-label escitalopram trial, using the Aberrant Behavior Checklist-Community Version (ABC-CV) score as an endpoint. There was no difference in outcomes for the different CYP450 genotype groups. However, UM participants showed a slower rate of change in dose over time.

In another study, Strawn and colleagues used pharmacokinetic (PK) parameters to model the dosing for escitalopram in different CYP450 genotypic groups. Based on PK modeling, poor metabolizers require a 10 mg/day dose and ultrarapid metabolizers require 30 mg/day to reach the equivalent 20 mg daily dose of normal metabolizers for similar drug exposure among the groups.

Finally, Aldrich and colleagues reported on a retrospective study of electronic medical record data from 263 youth aged younger than 19 years with anxiety and/or depressive disorders who were prescribed citalopram or escitalopram. As expected, patients with CYP2C19 PM genotypes had more adverse effects than CYP2C19 UM patients (P=0.015), including activation symptoms (P=0.029) and more rapid weight gain (P=0.018). In contrast, CYP2C19 PM patients discontinued treatment more frequently than CYP2C19 NM patients (P=0.007). Finally, faster metabolizers paradoxically responded more quickly (P=0.005) and trended toward less time spent in subsequent hospitalizations (P=0.06).

Databases for clinicians
The CPIC formed in 2009 as a joint collaboration between the Pharmacogenomics Research Network (PGRN) and the Pharmacogenomics Knowledgebase (PharmGKB). The PharmGKB, a National Institutes of Health-funded online knowledgebase, has been operating since 2000 to promote researchers’ understanding of the field of pharmacogenetics by serving as a database for storing peer-reviewed, freely accessible, genotype-based drug-dosing guidelines for clinicians.13

Another multidisciplinary group is the Dutch Pharmacogenetics Working Group (DPWG), which has developed pharmacogenetics-based therapeutic recommendations starting in 2005. Distinct gene-drug associations for well-known SSRIs have been catalogued by the DPWG (www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf). Although both CPIC and DPWG guidelines show a high level of concordance, differences exist, possibly due to different initial selection of the relevant gene-drug pairs or dissimilar allele classification with subsequent conflicting genotype to phenotype conversions.14

Conclusion
In summary, given that anxiety and depressive disorders in children are etiologically complex conditions, a full assessment and consideration for psychosocial treatments is a key first step in management. If medication management is indicated, the use of CYP450 has promise for real world use in pediatric patients with need for SSRI treatment. The current practice of starting at lower doses and increasing gradually is supported as a reasonable approach to the large majority of patients. In those patients with early toxic effects at lower dosing or lack of response with higher dosing, CYP450 genotyping may provide additional guidance. ■

For references, go to ContemporaryPediatrics.com/SSRI-for-children
A healthy 10-year-old male presents for evaluation with a 3-year history of an asymptomatic and progressive, mildly pruritic rash over his head and trunk. The first lesion appeared on his back 3 years ago, and numerous other lesions developed insidiously afterward. The patient’s father states that the lesions fade during the winter and become more prominent during the summer. Failed treatment included hydrocortisone.

Physical exam revealed well-circumscribed, annular, erythematous plaques with adherent scale and atrophy on the patient’s right forehead, cheeks, bilateral medial canthi, bilateral conchal bowls, and back (Figures 1 and 2). The rest of the physical exam was unremarkable. There was no recent travel, and the patient did not take any medications. There was no evidence of uveitis or arthritis.

Differential diagnosis
The initial differential diagnosis was broad given the nonspecific clinical presentation without significant symptoms (Table). Whereas granulomatous diseases such as granuloma annulare or sarcoidosis can present as infiltrated annular plaques, they generally lack the scale that is associated with disseminated cutaneous discoid lupus erythematosus (DLE). Lichen planus often has a shiny, violaceous hue, and hydroa vacciniforme often presents as small vesicles that heal with scarred, crusted erosions. Fungal acid-fast bacilli (AFB) and bacterial cultures help to eliminate any infectious etiologies. Biopsy helped to rule in or exclude possible neoplastic processes including cutaneous B-cell lymphoma.
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dermatology

Evaluation and testing

Punch biopsy from the patient’s back revealed prominent vacuolar change at the dermal-epidermal junction with hydropic degeneration of basal keratinocytes and numerous melanophages within the papillary dermis (Figures 3 and 4). Alcian blue staining revealed increased dermal mucin.

Blood work was unremarkable: C-reactive protein (CRP), 0.3; erythrocyte sedimentation rate (ESR), 11; complete blood count (CBC), normal; comprehensive metabolic panel (CMP), normal; antinuclear antibodies (ANA), negative; anti-double stranded DNA (anti-dsDNA), <1; anti-Ro/La, 0.2/<0.2; serum C3, 131; serum C4, 23; urinalysis, within normal limits (WNL).

Diagnosis

Given the clinical and histologic findings, this patient was diagnosed with DLE as more than one body segment was involved. Shortly after the labs returned, the patient’s mother revealed that she was recently diagnosed with lupus erythematosus (LE). This patient did not fulfill the American College of Rheumatology criteria for systemic lupus erythematosus (SLE) given the absence of laboratory abnormalities and systemic symptoms.

Discussion

The exact cause of DLE in this patient, as in most DLE patients, is unclear. There is a family history of LE, and pediatric DLE is more commonly associated with a genetic predisposition than in adult DLE. Sampaio and colleagues found that 11.8% of pediatric DLE patients had a family history of LE compared with 1% to 4.4% of adults. Several triggers can unmask native LE such as ultraviolet radiation exposure and tumor...
necrosis factor (TNF)-alpha antagonists. Although this patient has not used any medications, he is an active young boy who spends a great deal of time in the sun and is clearly photosensitive per his father.

Pediatric DLE is a rare condition predominantly affecting females. The clinical morphology and distribution are very similar to “classic” patterns seen in adults. The face and scalp are very common locations; scaling, hypertrophy, and follicular plugging with atrophy are frequent. Less than 3% of patients develop DLE before age 10 years. The risk of progression to SLE over time frame is approximately 25%. In one study, the risk to progression was greatest within the first year following a diagnosis of DLE.

There is general consensus between North American Dermatology and Rheumatology clinics that initial screening labs after diagnosis of DLE should include: CBCs with differential, urinalysis, complement levels, ESR, ANA, hepatic function tests, renal function/electrolytes, anti-dsDNA antibodies, as well as anti-Ro/SSA, anti-La/SSB, anti-Sm, and anti-RNP.

Compared with adults, pediatric DLE more commonly precedes SLE. Additionally, pediatric SLE is associated with a higher proportion of end-organ damage and is more frequently life threatening compared with the adult counterpart. All patients should be screened regularly through their entire lifetime given concern for progression to SLE.

**Patient outcome**

Sunscreen as photoprotection and topical corticosteroids were prescribed for this patient. Treatment with hydroxychloroquine is planned as the first-line systemic therapy. This medication would be cardioprotective, treat the cutaneous disease, reduce the likelihood of flares, and decrease autoantibody creation. Screening for hydroxychloroquine retinopathy should be done at baseline and then annually after 5 years of use in the majority of pediatric patients.

**FIGURE 3** Low power hematoxylin and eosin (H&E) staining with prominent vacuolar change at the dermal-epidermal junction with hydropic degeneration of basal keratinocytes.

**FIGURE 4** Higher-power hematoxylin and eosin (H&E) staining on higher magnification demonstrating prominent vacuolar change with hydropic degeneration of basal keratinocytes.
Pernio, or chilblains, is a chronic condition classically presenting as red-to-purple, edematous lesions of variable sizes on acral skin, typically fingers and toes. Lesions are commonly painful and pruritic, and they may progress to blisters and ulcers predisposing to infection. Symptoms result from abnormal vasoconstriction in response to physiologic stress, such as cold temperatures and hypoxemia.

The course may be acute, initiating as quickly as 24 hours following insult and improving within 3 weeks, or chronic, persisting or recurring over weeks to months despite lack of repeated insults. One-third of patients show at least 1 laboratory abnormality that may raise concern for underlying hematologic or rheumatologic disease. Patients with secondary perniosis due to such conditions are more likely to present with chronic symptoms.

Differential diagnosis and workup
The differential diagnosis for pernio includes leukocytoclastic vasculitis, Henoch-Schonlein Purpura, and hand-foot-mouth disease. Chilblains lupus erythematosus is an uncommon disorder that presents with both the characteristic discoid papules of cutaneous lupus erythematosus as well as the lesions of pernio. A complete history that includes recent illnesses, medications, triggers, and other involved organs is vital to the diagnosis of pernio.

THE CASE
A healthy 15-year-old girl presents for evaluation of itchy, painful bumps on her toes that developed 3 weeks earlier. The bumps become more numerous and bothersome when she is outdoors sledding and skiing.

FIGURE 1 Erythematous-to-violaceous, indurated papules and small plaques on the dorsal toes were tender to palpation.
dermatology

Though not required, skin biopsy may be utilized when the diagnosis is unclear. Supporting histopathology shows papillary dermal edema with lymphocytic infiltrate surrounding blood vessels and adnexal structures. Laboratory workup includes a complete blood count (CBC) and antinuclear antibody (ANA) titers to rule out underlying hematologic or rheumatologic abnormalities.

Management
First-line management for pernio involves keeping extremities warm and dry. Medium-to-high potency topical corticosteroids are thought to be beneficial in clinical practice, however, no large, randomized trials have investigated their effectiveness. The vasodilatory calcium channel blocker nifedipine used for 6 weeks may alleviate symptoms, although evidence for its efficacy is conflicting.

Review and examination
Review of systems for this patient included frequent discoloration and loss of sensation in the hands and feet during winter months. She denied foot trauma, lesions elsewhere on her body, recent infection, new medications, abdominal pain, chills, and joint pains.

Examination revealed erythematous-to-violaceous, edematous papules and small plaques on the dorsal feet with greatest density on the toes (Figure 1). Laboratory studies revealed positive ANA (1:320) with speckled pattern and normal CBC, erythrocyte sedimentation rate, C-reactive protein, C3, C4, anti-Smith, antidualle-stranded DNA, anti-Ro, and anti-La antibodies. Biopsy showed mild subepidermal edema with brisk perivascular and periadnexal lymphocytic infiltrate (Figure 2).

Patient outcome
The patient was diagnosed with pernio based on clinical history and biopsy results. Despite her ANA results, she did not meet criteria for any form of lupus erythematosus. She was counseled on keeping her hands and feet dry and wearing insulated gloves and footwear.

Two months later, her symptoms improved with onset of warmer weather. Two years later, despite continued conservative management, her symptoms recurred. Clobetasol ointment twice daily for no more than 2 consecutive weeks was prescribed. The lesions cleared within 6 months.

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Dr Cohen, section editor for Dermcase, is professor of Pediatrics and of Dermatology, Johns Hopkins University School of Medicine, Baltimore, Maryland. The authors and section editor 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 allow the authors and editor to focus on key teaching points. Images also may be edited or substituted for teaching purposes.

For references, go to ContemporaryPediatrics.com/dermcase-1119

**FIGURE 2** Punch biopsy of a discrete papule revealed mild subepidermal edema and a prominent perivascular and periadnexal lymphocytic infiltrate.
NEXPLANON can help prevent unintended pregnancy in postmenarchal adolescent patients*

- Safety and efficacy of NEXPLANON have been established in women of reproductive age and are expected to be the same for postpubertal adolescents
- No clinical studies have been conducted in women younger than 18 years. Use of this product before menarche is not indicated

NEXPLANON is placed subdermally just under the skin of the inner upper arm

Up to 3 years of pregnancy prevention† >99% effective‡ Reversible if her plans change

*The ability of minors to consent to the provision of medical or surgical care or services by a health care practitioner may vary by state. Practitioners should receive appropriate consent, including the consent of parents/guardians where required, prior to insertion or removal of NEXPLANON.
†NEXPLANON must be removed by the end of the third year and may be replaced by another NEXPLANON at the time of removal, if continued contraceptive protection is desired.
‡Less than 1 pregnancy per 100 women who used NEXPLANON for 1 year.

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON
- NEXPLANON should not be used in women who have known or suspected pregnancy; current or past history of thrombosis or thromboembolic disorders; liver tumors, benign or malignant, or active liver disease; undiagnosed abnormal genital bleeding; known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past; and/or allergic reaction to any of the components of NEXPLANON.

Complications of insertion and removal
- NEXPLANON should be inserted subdermally and be palpable after insertion. Palpate immediately after insertion to ensure proper placement. Undetected failure to insert the implant may lead to unintended pregnancy. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.
- Insertion and removal-related complications may include pain, paresthesias, bleeding, hematoma, scarring, or infection. If NEXPLANON is inserted too deeply (intramuscular or in the fascia), neural or vascular injury may occur. Implant removal may be difficult or impossible if the implant is not inserted correctly, inserted too deeply, not palpable, encased in fibrous tissue, or has migrated. If at any time the implant cannot be palpated, it should be localized and removal is recommended.
- There have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. Endovascular or surgical procedures may be needed for removal.

NEXPLANON and pregnancy
- Be alert to the possibility of an ectopic pregnancy in women using NEXPLANON who become pregnant or complain of lower abdominal pain.
- Rule out pregnancy before inserting NEXPLANON.

Educate her about the risk of serious vascular events
- The use of combination hormonal contraceptives increases the risk of vascular events, including arterial events (stroke and myocardial infarction [MI]) or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis [DVT], retinal vein thrombosis, and pulmonary embolism). Women with risk factors known to increase the risk of these events should be carefully assessed. Postmarketing reports in women using etonogestrel implants have included pulmonary emboli (some fatal), DVT, MI, and stroke. NEXPLANON should be removed if thrombosis occurs.
- Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum.
- Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. Consider removing the NEXPLANON implant in case of long-term immobilization due to surgery or illness.
Consider NEXPLANON for your appropriate postmenarchal adolescent patients*

In 2013, according to the Guttmacher Institute, 1 in 10 sexually active adolescent girls in the US became pregnant†

The American Academy of Pediatrics (AAP) recommends counseling on a broad range of appropriate contraceptive options. LARCs, including the progestin implant and IUDs, should be considered first-line contraceptive choices for adolescents.‡

NEXPLANON is the only non-uterine Long-Acting Reversible Contraceptive (LARC)

Counts of pregnancies include births, legal induced abortions and spontaneous fetal losses (ie, miscarriages and stillbirths). The National Center for Health Statistics (NCHS) provides annual counts of births in the United States, as reported in the National Vital Statistics System (via birth certificates). We applied the percentage of women aged 15–19 reporting ever having had sexual intercourse to population totals of women in that age range in each year to calculate the number who were sexually experienced.†

SELECTED SAFETY INFORMATION (continued)

Counsel her about changes in bleeding patterns

- Women are likely to have changes in their menstrual bleeding pattern with NEXPLANON, including changes in frequency, intensity, or duration. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy. In clinical studies of the non-radiopaque etonogestrel implant, changes in bleeding pattern were the most common reason reported for stopping treatment (11.1%). Counsel women regarding potential changes they may experience.

Be aware of other serious complications, adverse reactions, and drug interactions

- Remove NEXPLANON if jaundice occurs.
- Remove NEXPLANON if blood pressure rises significantly and becomes uncontrolled.
- Prediabetic and diabetic women using NEXPLANON should be carefully monitored.
- Carefully observe women with a history of depressed mood. Consider removing NEXPLANON in patients who become significantly depressed.
- The most common adverse reactions (≥10%) reported in clinical trials were headache (24.9%), vaginitis (14.5%), weight increase (13.7%), acne (13.5%), breast pain (12.8%), abdominal pain (10.9%), and pharyngitis (10.5%).
- Drugs or herbal products that induce enzymes, including CYP3A4, may decrease the effectiveness of NEXPLANON or increase breakthrough bleeding.
- The efficacy of NEXPLANON in women weighing more than 130% of their ideal body weight has not been studied. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. Therefore, NEXPLANON may be less effective in overweight women.
- Counsel women to contact their health care provider immediately if, at any time, they are unable to palpate the implant.
- NEXPLANON does not protect against HIV or other STDs.

Please read the adjacent Brief Summary of the Prescribing Information.

The efficacy of NEXPLANON does not depend on daily, weekly, or monthly administration. All healthcare providers should receive instruction and training prior to performing implantation and/or removal of NEXPLANON. A pulse technique is used to insert subdermally just under the skin at the inner aspect of the non-dominant upper arm. The insertion site is overlaying the biceps muscle about 8-10 cm (3-4 inches) from the mid-epicondyle of the humerus and 3-3.5 cm (1.25-2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. An implant inserted more deeply than subdermally may indent the subcutaneous tissue under the skin at the inner aspect of the non-dominant upper arm. The implant should be palpable immediately after insertion. Undetected failure to insert the implant may be difficult to diagnose. Complications related to implantation and removal procedures, such as pain, inflammation, bleeding, hematoma, scarring, or infection, may occur.

Several findings have been reported in women using the non-radiopaque etonogestrel implant (IMPLANON)[etonogestrel implant] and/or NEXPLANON, other progestin-only contraceptives, or everolimus with the aromatase inhibitor (anastrozole or exemestane) in postmenopausal women. These include:

- Complications of Insertion and Removal
- Bleeding Irregularities
- Fluid Retention
- Hypertension
- Breast and Reproductive Organs
- Neurovascular Injury
- Other Adverse Reactions

In the event of a bleeding pattern that is different from those reported here, healthcare providers should be aware of the possibility of a recurrence. Evaluate for retinal vein thrombosis immediately if there is unexplained loss of vision, proptosis, diplopia, papiledema, or retinal vascular lesions. Consider removal of the NEXPLANON implant in cases of long-standing immobilization due to surgery or illness.

**Liver Disease**

Disturbances of liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal. Women using NEXPLANON who become pregnant or complain of lower abdominal pain. Women using NEXPLANON who become pregnant or complain of lower abdominal pain. Women using NEXPLANON who become pregnant or complain of lower abdominal pain. Women using NEXPLANON who become pregnant or complain of lower abdominal pain. Women using NEXPLANON who become pregnant or complain of lower abdominal pain. Women using NEXPLANON who become pregnant or complain of lower abdominal pain. Women using NEXPLANON who become pregnant or complain of lower abdominal pain.

Women with a history of hyper tension-related diseases or renal disease should be discouraged from using hormonal contraception. For women with well-controlled hypertension, use of NEXPLANON can be considered. Women with hypertension using NEXPLANON should be closely monitored. If sustained hypertension develops during the use of NEXPLANON, or if a significant increase in blood pressure does not respond adequately to antihypertensive therapy, NEXPLANON should be removed.

**Gallbladder Disease**

A non-radiopaque etonogestrel implant is associated with a small increased relative risk of developing gallbladder disease among women using hormonal contraception. Women using etonogestrel implants should be monitored for clinical symptoms of gallbladder disease. NEXPLANON may be a risk factor for the development of a recurrence. Evaluate for gallbladder disease immediately if there is unexplained right upper quadrant pain, distension, fever, or jaundice. Consider removal of the NEXPLANON implant in cases of long-standing immobilization due to surgery or illness.

**Carcinoma of the Breast and Reproductive Organs**

Breast cancer is contraindicated in women who are breastfeeding. Breast cancer is hormonally sensitive. Breast cancer may be hormonally sensitive. Breast cancer may be hormonally sensitive.

**Carcinoma of the Breast and Reproductive Organs**

Breast cancer is hormonally sensitive. Breast cancer may be hormonally sensitive. Breast cancer may be hormonally sensitive.

**Adverse Reactions**

In clinical trials of the non-radiopaque etonogestrel implant (IMPLANON), bleeding patterns ranged from amenorrhea (1 in 5 women) to frequent and/or prolonged bleeding (1 in 5 women). The bleeding pattern experienced during the first three months of insertion. In cases where the implant has migrated to the pulmonary artery, endovascular or surgical procedures may be needed for removal.

- **Bleeding**
- **Irregularities**
- **Thrombotic and Other Vascular Events**
- **Hypertension**
- **Fluid Retention**
- **Other Adverse Reactions**

**Table 2: Bleeding Patterns Using the Non-Radiopaque Etonogestrel Implant (IMPLANON) During the First 2 Years of Use**

<table>
<thead>
<tr>
<th>Bleeding Patterns</th>
<th>Definitions</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ineffective</td>
<td>Less than three bleeding and/or spotting episodes in 90 days (including amenorrhea)</td>
<td>33.6</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>No bleeding and/or spotting in 90 days</td>
<td>22.2</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Any bleeding and/or spotting episode lasting more than 14 days in 90 days</td>
<td>17.7</td>
</tr>
<tr>
<td>Frequent</td>
<td>More than 5 bleeding and/or spotting episodes in 90 days</td>
<td>6.7</td>
</tr>
</tbody>
</table>

**Warning and Precautions**

The following information is based on experience with the etonogestrel implants (IMPLANON[etonogestrel implant] and/or NEXPLANON), other progestin-only contraceptives, or everolimus with the aromatase inhibitor (anastrozole or exemestane) in postmenopausal women. These include:

- **Complications of Insertion and Removal**
- **Bleeding Irregularities**
- **Fluid Retention**
- **Hypertension**
- **Other Adverse Reactions**

Women should be counseled regarding the bleeding pattern changes they may experience so that they know what to expect. Abnormal bleeding should be evaluated as needed to exclude pathological conditions or pregnancy. In clinical studies of the non-radiopaque etonogestrel implant, reports of changes in bleeding pattern were the most common reason for stopping treatment (11.1%). Irregular bleeding (10.6%) was the single most common reason for stopping treatment, while amenorrhea (0.3%) was cited less frequently. In these studies, women had an average of 17.7 days of bleeding or spotting every 90 days (based on 3,315 intervals of 90 days recorded by 780 patients). The percentages of patients having 0, 1-7, 8-21, or more than 21 days of bleeding or spotting every 90 day interval while using the non-radiopaque etonogestrel implant are shown in Table 1.

<table>
<thead>
<tr>
<th>Total Days of Spotting or Bleeding</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Days 91-180 (N = 745)</td>
<td>Treatment Days 271-360 (N = 697)</td>
</tr>
<tr>
<td>0 days</td>
<td>19%</td>
</tr>
<tr>
<td>1-7 days</td>
<td>15%</td>
</tr>
<tr>
<td>8-21 days</td>
<td>35%</td>
</tr>
<tr>
<td>&gt;21 days</td>
<td>35%</td>
</tr>
</tbody>
</table>

Bleeding patterns observed with use of the non-radiopaque etonogestrel implant for up to 2 years, and the proportion of 90-day intervals with these bleeding patterns, are summarized in Table 2.
Fluid Retention

Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.

Contact Lenses

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

In Situ Broken or Bent Implant

There have been reports of broken or bent implants while in the patient’s arm. Based on in vitro data, when an implant is broken or bent, the release rate of etonogestrel may be slightly increased. When an implant is removed, it is important to remove it in its entirety [see Dosage and Administration].

Monitoring

A woman who is using NEXPLANON should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.

Drug-Laboratory Test Interactions

Sex hormone-binding globulin concentrations may be decreased for the first six months after NEXPLANON insertion followed by gradual recovery. Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

ADVERSE REACTIONS

In clinical trials involving 942 women who were safely evaluated, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPLANON® [etonogestrel implant] (111% of women). Adverse reactions that resulted in a rate of discontinuation of ≥1% are shown in Table 3.

Table 3: Adverse Reactions Leading to Discontinuation of Treatment in 1% or More of Subjects in Clinical Trials of the Non-Radiopaque Etonogestrel Implant (IMPLANON®)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Studies</th>
<th>N-942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding irregularities*</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>Emotional lability†</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Weight increase</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>3.3%</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>1.0%</td>
<td></td>
</tr>
</tbody>
</table>

Includes "frequent", "brief", "prolonged", "spotting", and other patterns of bleeding irregularity

*Among US subjects (N=330), 6.1% experienced emotional lability that led to discontinuation.

†Among US subjects (N=330), 2.4% experienced depression that led to discontinuation.

Other adverse reactions that were reported by at least 5% of subjects in the non-radiopaque etonogestrel implant clinical trials are listed in Table 4.

Table 4: Common Adverse Reactions Reported by ≥5% of Subjects in Clinical Trials With the Non-Radiopaque Etonogestrel Implant (IMPLANON®)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Studies</th>
<th>N-942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>24.9%</td>
<td></td>
</tr>
<tr>
<td>Vaginitis</td>
<td>14.5%</td>
<td></td>
</tr>
<tr>
<td>Weight increase</td>
<td>13.7%</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>13.5%</td>
<td></td>
</tr>
<tr>
<td>Breast pain</td>
<td>12.8%</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10.9%</td>
<td></td>
</tr>
<tr>
<td>Fibrocystic breast</td>
<td>10.5%</td>
<td></td>
</tr>
<tr>
<td>Leukorrhea</td>
<td>9.8%</td>
<td></td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>7.6%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.2%</td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>7.2%</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>6.8%</td>
<td></td>
</tr>
<tr>
<td>Emotional lability</td>
<td>6.5%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6.4%</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>5.5%</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>5.4%</td>
<td></td>
</tr>
<tr>
<td>Insertion site pain</td>
<td>5.2%</td>
<td></td>
</tr>
</tbody>
</table>

In a clinical trial of NEXPLANON, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8.6% of women. Erythema was the most frequent implant site complication, reported during and/or shortly after insertion, occurring in 3.3% of subjects. Additionally, hematoma (3.0%), bruising (2.0%), pain (1.0%), and swelling (0.7%) were reported.

Effects of Other Drugs on Hormonal Contraceptives

Substances decreasing the plasma concentrations of hormonal contraceptives (HCS) and potentially diminishing the efficacy of HCS: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of HCs and potentially diminish the effectiveness of HCs include rifampin, rifabutin, carbamazepine, bosentan, felbamate, griseofulvin, oxicam derivatives, nicotinamide, flavonoids, grapefruit juice, or ketocazole may increase the serum concentrations of progestins, including etonogestrel.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of protease have been noted in cases of co-administration with HCV protease inhibitors (decrease, e.g., nelafavir, ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ ritonavir, and saquinavir/ritonavir) or non-nucleoside reverse transcriptase inhibitors (increase, e.g., efavirenz, nefazodone) or other drugs (increase, e.g., efavirenz). These changes may become clinically relevant in some cases. Consult the prescribing information of antiretroviral and anti-retroviral concomitant medications to identify potential interactions.

Effects of Hormonal Contraceptives on Other Drugs

Hormonal contraceptives may affect the metabolism of other drugs. Consequently, plasma concentrations may either increase (for example, cyclosporine) or decrease (for example, lamotrigine). Consult the listing of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

NEXPLANON is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant [see Contraindications]. Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following maternal exposure to low dose GCs prior to conception or during early pregnancy. In a non-developmentally adverse pregnancy, certain conditions were observed in response of a specific drug, gestational age, and maternal health.

Lactation

Risk Summary

Small amounts of contraceptive steroids and/or metabolites, including etonogestrel are present in human milk. No significant adverse effects have been observed in the production or quality of breast milk, or on the physical and psychomotor development of breastfed infants. Hormonal contraceptives, including etonogestrel, can reduce milk production in breastfeeding mothers. This is less milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it may occur at any time in some women. When possible, advise the nursing mother about both hormonal and non-hormonal contraceptive options, as some may not be the initial choice for these patients. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NEXPLANON and any potential adverse effects on the breastfed child from NEXPLANON or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of NEXPLANON have been established in women of reproductive age. Safety and efficacy of NEXPLANON are expected to be the same for postpubertal adolescents. No clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.

Geriatric Use

This product has not been studied in women over 65 years of age and is not indicated in this population.

Hepatic Impairment

No studies were conducted to evaluate the effect of hepatic disease on the disposition of NEXPLANON. The use of NEXPLANON in women with active liver disease is contraindicated [see Contraindications].

Overweight Women

The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

OVERDOSAGE

Overdose may result if more than one implant is inserted. In case of suspected overdose, the implant should be removed.

NONCLINICAL TOXICOLOGY

In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day (equal to approximately 1.8-3.6 times the systemic steady state exposure in women using NEXPLANON), no drug-related carcinogenic potential was observed. Etonogestrel was not genotoxic in the in vitro Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the in vivo mouse micronucleus test. Fertility in rats returned after withdrawal from treatment.

PATIENT COUNSELLING INFORMATION

See FDA-Approved Patient Labeling.

- Counsel women about the insertion and removal procedure of the NEXPLANON implant. Provide the woman with a copy of the Patient Labeling and ensure that she understands the information in the Patient Labeling before insertion and removal. A USER CARD and consent form are included in the packaging. Have the woman complete a consent form and retain it in your records. The USER CARD box will be filled out and given to the woman after insertion of the NEXPLANON implant so that she will have a record of the location of the implant in the upper arm and when it should be removed.
- Counsel women to contact their healthcare provider immediately if, at any time, they are unable to palpate the implant.
- Counsel women that NEXPLANON does not protect against HIV infection (AIDS) or other STDs.
- Counsel women that the use of NEXPLANON may be associated with changes in their normal menstrual bleeding patterns so that they know what to expect.

Manufactured for: Merck & Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ 08889, USA.

For more detailed information, please read the Prescribing Information.

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How to strengthen PCPs’ mental health training

A new nationwide program helps primary care providers (PCPs) with mental health training to better address routine psychosocial issues in children and their families.

MOLLIKA SAJADY, DO, MPH; EMILY BORMAN-SHOAP, MD; KATHERINE E MURRAY, MD, MPH; JONATHAN HOMANS, MD; ANDREW BARNES, MD, MPH

To address this growing concern, the US Department of Health and Human Services’ Health Resources and Services Administration (HRSA), Maternal and Child Health Bureau (MCHB) Division of Maternal and Child Health, provides funding for 10 programs nationwide to address the mental health-training gap and support the professional development of PCPs, known as collaborative office rounds (COR).

Program highlights
All COR programs are structured as regularly scheduled discussion groups, co-led by developmental-behavioral pediatricians and child and adolescent psychiatrists, with the aim of increasing the comfort level and ability of PCPs to address routine psychosocial issues of children, adolescents, and their families. Participants include interdisciplinary community practitioners and trainees in fields such as medicine, psychology, dentistry, and social work. Most COR programs provide continuing education credits to participants.

MAIN GOALS
There are 5 primary goals of the University of Minnesota COR program, as follows:

GOAL 1: Enhance PCP understanding of psychosocial aspects of child development, disorders, and disability.

GOAL 2: Increase provider availability to help children and families address these issues.

GOAL 3: Expand the provider’s ability to distinguish between transient disturbances and more serious psychiatric disorders that may require referral.

Dr Sajady is a developmental-behavioral pediatric fellow physician at the University of Minnesota, Minneapolis, Minnesota.

Dr Borman-Shoap is an assistant professor of Pediatrics, vice chair of Education, and program director, Pediatric Residency Program, University of Minnesota, Minneapolis.

Dr Murray is an assistant professor of Developmental-Behavioral Pediatrics, University of Minnesota, Minneapolis.

Dr Homans is an assistant professor of Psychiatry and associate program director, Child and Adolescent Psychiatry Fellowship, University of Minnesota, Minneapolis.

Dr Barnes is an assistant professor of Developmental-Behavioral Pediatrics and program director, Developmental-Behavioral Pediatric Fellowship, University of Minnesota, Minneapolis.
GOAL 4: Promote collaboration among PCPs with developmental-behavioral pediatricians and child and adolescent psychiatrists.

GOAL 5: Facilitate a comprehensive approach to health supervision, such as outlined in Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents.⁴

PROGRAM DESIGN

The University of Minnesota COR program was first established in 1996 and is designed as a biweekly-to-monthly case-based discussion addressing a real-world clinical dilemma selected by a community professional. A PCP chooses a challenging case to highlight from his/her practice, filling out a brief standardized online form that includes questions that the provider wants the group to address/assist with; age and presenting problems; developmental, academic, and past medical, social, and family histories; cultural and linguistic considerations; current services and interventions; initial diagnostic formulation and assessment; and relevant follow-up visit information (Table 1). The resulting de-identified case summary is sent electronically to participants 3 days prior to the meeting.

At the beginning of the one-hour session, COR participants (usually 10 to 20 persons) offer brief introductions of themselves to better understand the various health professions represented. Additional virtual options to participate via phone or video call are offered as well. The presenter then verbally summarizes the case over approximately 15 minutes.

After the case is presented, participants ask clarifying questions before dividing into facilitated small groups of 4 to 6 persons for discussion of the case and to address the questions brought forth by the presenter. After 15 to 20 minutes of small group discussion, the entire group reconvenes for a larger discussion of the case for the remainder of the time. At least one representative from each small group summarizes the points discussed and offers any recommendations or resources for the presenter to consider for ongoing care of the patient.

Examples of COR discussions that have been presented at the University of Minnesota are provided in Table 2.

The COR program at the University of Minnesota was recently highlighted in the media by Minnesota Public Radio, as mental health training is becoming

### TABLE 1. COR CASE INFORMATION FORM

<table>
<thead>
<tr>
<th>PREFACE QUESTIONS</th>
<th>CASE TITLE</th>
<th>LIST 2-5 QUESTIONS YOU’D LIKE TO CONSIDER AT COR FOR THIS CASE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient’s age and presenting problems (please do not use real names or include identifying information). Example: “J. is a 10-year-old boy with historical diagnosis of ADHD and dyslexia who became severely irritable on 10 mg of daily methylphenidate 2 months prior to my first visit with him and it was discontinued. His parents wanted to reconsider medication options.”</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Developmental history (including summary of results of developmental, behavioral, mental health screening or psychological testing, if done).</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Academic history (including academic accommodations and modifications, school-based services/therapies, and whether a 504 or IEP is in place).</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Current services and therapies (outside school).</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Current medications (including doses, if known).</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Past medical history (including birth history, if known).</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Social history (including sociodemographic risk factors, adverse childhood experiences, resilience factors, and cultural-linguistic factors).</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Family history.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Vital signs (including height, weight, body mass index percentile estimates, if known).</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Behavioral observations (including caregiver-child interactions).</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Relevant exam findings.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Initial diagnostic formulation/assessment.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Initial clinical decision-making/management plan.</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Relevant subsequent clinical course.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COR, collaborative office rounds; IEP, individualized education program.

Author created.
an increasingly important public health concern. A unique aspect of the University of Minnesota COR program is our emphasis on hosting a conference that is geared toward providers in practices in conjunction with residents in training. In this way, primary care preceptors are encouraged to participate with their continuity clinic trainees by selecting a comanaged case for presentation. Discussing cases with providers with a range of experience levels provides rich opportunities for shared learning.

GUIDING PRINCIPLES
During each COR session there are 4 guiding principles that are followed:
1. Focus upon practitioners’ presentation of common clinical dilemmas.
2. Create a common language and supportive environment.
3. Enhance understanding of psychosocial aspects of child development, emotional and behavioral disorders, and disabilities, and the ability of providers to help families cope.
4. Increase the providers’ ability and comfort to differentiate transient from more severe disorders. Both prospective and retrospective analytical approaches are utilized to promote understanding of the case and plan for optimum care moving forward.

PROGRAM EVALUATION
The COR program at the University of Minnesota also collects quantitative and qualitative feedback for continuous quality improvement. Over 90% of participants reported that COR meetings met the program objectives well and most participants stated that they would continue to attend COR in the future (64.7% of respondents).

Some examples of general comments about the University of Minnesota COR program from attendees include: “a great opportunity to engage with peers”; “interactive and designed to address meaningful clinical problems”; and “convenient and free.” Suggestions for improvement include: “cases with effects of technology on children with autism”; and “ethics cases and challenges with medication management.”

Lessons learned
Challenges faced by our COR program include recruiting community providers outside the university to attend the sessions and lower participation numbers for monthly morning community sessions compared with monthly residency training-based lunch sessions. To increase participation, we have combined the community and residency training sessions into one monthly lunch session (with food provided), while offering virtual participation options. We encourage community clinics to block an hour of time for their clinicians to participate in COR monthly. Finally, we are exploring ways to help physicians to gain Maintenance of Certification (MOC) credit for COR participation.

Key takeaways
The COR program at the University of Minnesota is a case-based continuing-education initiative funded by the MCHB to address mental health training gaps for PCPs. Other programs could use the COR model to provide ongoing education and encourage collaboration among PCPs, primary care trainees, and mental health professionals.

Table 2

<table>
<thead>
<tr>
<th>COR CASE TITLE EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Culturally Bound Barriers in Mental Health Care: A Somali Case Presentation&quot;</td>
</tr>
<tr>
<td>&quot;ADHD Evaluation in a Homeschooled Fifth Grader&quot;</td>
</tr>
<tr>
<td>&quot;Severe Aggression and Impulsive Behavioral Concerns in a 2-Year-Old: Do Medications Play a Role in the Treatment Plan?&quot;</td>
</tr>
<tr>
<td>&quot;Kicked Out of Daycare: What to do Now?&quot;</td>
</tr>
<tr>
<td>&quot;Behavioral Struggles in a 9-Year-Old with an All-Star Team&quot;</td>
</tr>
<tr>
<td>&quot;6-Year-Old with Concerns About Violent Behavior at School&quot;</td>
</tr>
<tr>
<td>&quot;Adolescent Paraphilia in the Internet Age&quot;</td>
</tr>
<tr>
<td>&quot;Groundhog Day with School-Triggered Anxiety&quot;</td>
</tr>
<tr>
<td>&quot;13-Year-Old Girl Presenting with Headache&quot;</td>
</tr>
<tr>
<td>&quot;Medication Adherence in an Adolescent Patient with High-Functioning Autism: How to Communicate?&quot;</td>
</tr>
<tr>
<td>&quot;Would This Have Happened to My Son? The Admission Course of a 6-Year-Old with Auditory Hallucinations Due to Psychostimulant Medication&quot;</td>
</tr>
<tr>
<td>&quot;4-Year-Old Girl with Anxiety at a Well-Child Check&quot;</td>
</tr>
<tr>
<td>&quot;Life After a Second Suicide Attempt&quot;</td>
</tr>
<tr>
<td>&quot;6-Year-Old Boy with ADHD and Aggressive Behaviors at School&quot;</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COR, collaborative office rounds. Author created.
Novel study connects family stress to asthma exacerbation

In a new study published in *Pediatrics*, principal Investigator Molly Martin, MD, MAPP, associate professor of Pediatrics in the University of Illinois at Chicago (UIC) College of Medicine and fellow of the Institute for Health Research and Policy, and her team reveal that family chaos corresponded to worse asthma control, even when accounting for parent and child depression.

"Much research has shown a link between psychosocial issues and child asthma control, says Sally Weinstein, PHD, associate director of the University of Illinois Center on Depression and Resilience, associate professor of Clinical Psychology at the UIC College of Medicine, and lead author of the report, but these links are not well understood. "We do not have great answers to the questions of 'why' and 'how' this relationship exists," Weinstein says. "Our aim was to address some of these gaps in the literature and our understanding of the health disparities that exist in pediatric asthma, particularly in low-income minority populations, by examining family chaos as a potential pathway that could explain the link between parent/child mental health and child asthma control."

The study shows that there are many factors to asthma manifestation and control, she adds. "Parent, child, and family factors all play a role in the etiology and maintenance of child asthma control," says Weinstein. "Above and beyond the effects of parent and child depression, family chaos emerged as a robust influence on child asthma outcomes in an urban, high-risk population."

The study is the first to suggest that family chaos is indeed a powerful mechanism linking parent depression and worse child asthma control in a high-risk urban population," Weinstein adds.

"Because it’s a first-of-its-kind study, this study offers a fresh perspective of exploring the psychosocial risk factors of asthma and opens up the opportunity to equip front line providers such as pediatricians, community health workers, and parents and caregivers with guidance and a resource to develop and advance a collaborative system of care for asthma management," she says.

Still, Weinstein says knowing the problem is the first step in finding a solution.

“Our findings offer a much-needed resource to more effectively control pediatric asthma in high-risk populations—integrating behavioral interventions that can improve family chaos through developing family routines, structure, and organization, particularly around asthma management,” Weinstein says.

Asthma is a difficult condition to control, and this research could point the way to more effective treatment methods, she adds. Weinstein says whereas the findings of the study are novel, they were not all that surprising.

“Despite all our advances in treatment, child asthma prevalence and morbidity remain high. What was most compelling about this study was that focusing on the family can be key to improving child asthma,” Weinstein says. “As a child psychologist, I suppose that I’m not surprised that family functioning plays such a
respiratory

Are sleep studies helpful for treating sleep apnea?

MIRANDA HESTER, EDITOR

Polysonmography has long been considered key to diagnosing obstructive sleep apnea (OSA) in children, but a new study in Pediatrics questions how helpful the technique is for determining whether a child will benefit from an adenotonsillectomy.

Researchers obtained cognitive, behavioral, quality-of-life, health, and polysomnographic outcomes at baseline and at 7 months from the Childhood Adenotonsillectomy Trial, a randomized trial that compared the outcomes of watchful waiting and early adenotonsillectomy in children who have OSA.

The study included 398 children aged 5 to 9 years. At follow-up, 244 children (61%) saw resolution of OSA. A polysomnographic resolution of OSA accounted for small but significant proportions of changes in disease-specific quality of life (proportion mediated, 0.11 [95% confidence interval (CI), 0.04 to 0.20]; P=.004) and symptoms (proportion mediated, 0.13 [95% CI, 0.07 to 0.21]; P<.001). A change in polysomnographic severity also showed a similar mediation in disease-specific quality-of-life outcomes (proportion mediated, 0.20 [95% CI, 0.10 to 0.31]; P=.004). However, in the other 16 outcomes, there was no significant mediation effect identified. Adenotonsillectomy was found to return a normal polysomnography in 79% of children versus 46% who underwent watchful waiting. Obstructive sleep apnea resolved in roughly 50% of the children who underwent watchful waiting.

The researchers concluded that most of the treatment-related changes in the outcomes of OSA in school-aged children were not causally attributable to polysomnographic resolution or changes in its severity. They said the results illustrate the limited use of polysomnographic thresholds for managing childhood OSA.

Although this study focused only on pediatric asthma, Weinstein couldn’t say whether family chaos contributes to other chronic conditions in the pediatric population.

“Family routines and structure are important for child and family well-being, and that relationship becomes even more important when the family is confronted with the challenges involved in managing a chronic health condition,” Weinstein explains. “Our findings point to the importance of future research exploring the role of family chaos in other pediatric chronic conditions that require daily management.”

For reference, go to
ContemporaryPediatrics.com/
family-stress-and-asthma

For reference, go to
ContemporaryPediatrics.com/
polysomnography-for-OSA

key role in child asthma outcomes, yet this is the first study to document this relationship.”

Weinstein says the study highlights the importance of caring for the whole child as well as their families.

“Our research underscores the importance of looking beyond symptoms in children with uncontrolled asthma to address the health and well-being of the child, caregiver, and the family,” she says. “Our findings suggest that assessing and addressing child and parent depression is critical for improving child asthma outcomes in high-risk populations. Additionally, offering education and support on family structure, organizations, and routines in the household around asthma management may be particularly important tools for the healthcare provider.”

Pediatricians are a vital frontline provider for children and their caregivers, Weinstein adds, and should include parents in some way in their routine assessments. “Including brief, low-burden assessments of parental well-being in routine child visits, followed by providing mental health resources and referrals to parents identified as higher risk, can offer an important gateway for parents to access their own mental healthcare,” Weinstein says. “Having a list of local resources for mental health treatment, with a few guidance points on what to ask for and what information may be needed to schedule an appointment, available for parents may help break down barriers associated with accessing mental health resources.”

Although this study focused only on pediatric asthma, Weinstein couldn’t say whether family chaos contributes to other chronic conditions in the pediatric population.

“Family routines and structure are important for child and family well-being, and that relationship becomes even more important when the family is confronted with the challenges involved in managing a chronic health condition,” Weinstein explains. “Our findings point to the importance of future research exploring the role of family chaos in other pediatric chronic conditions that require daily management.”
Pediatric hypertension criteria should reflect overweight and obesity

A European study reveals that obesity criteria used by the American Academy of Pediatrics to diagnose pediatric hypertension helps identify more children at risk of cardiovascular disease.

RACHAEL ZIMLICH, RN, BSN

Criteria to classify children and young adults as hypertensive should be changed to reflect the status of overweight and obese children with high blood pressure who don’t meet current guidelines, according to a recent report.

The recommendation was made in a study published in the European Journal of Preventive Cardiology, and suggests that the European Society of Hypertension (ESH) criteria—last updated in 2016—must be updated again to address the increased cardiovascular risk faced by overweight and obese teenagers currently considered nonhypertensive under current ESH guidelines.1

The study evaluated children and teenagers aged 6 to 16 years who were overweight or obese and classified as nonhypertensive under current ESH guidance. Researchers applied both ESH criteria from 2016 and American Academy of Pediatrics (AAP) guidelines from 2017 to these children and teenagers, considering additional cardiovascular and health information. When AAP criteria were applied to the study group, 11% were classified as hypertensive. These participants tended to be older with lower high-density lipoprotein levels, higher body mass index, and other risk factors when compared with those participants who were classified as nonhypertensive under both current ESH and AAP criteria.

Additionally, researchers note that children and adolescents who fell into the hypertensive group when AAP criteria were applied—but continued to be nonhypertensive under ESH criteria—had greater insulin resistance, high total cholesterol to HDL-C ratios, and higher rates of left ventricular hypertrophy.

The researchers suggest that by adapting ESH criteria to better match current AAP criteria, more high-risk children and teenagers could benefit from early identification of hypertension and better avoidance of the progression of cardiovascular damage.

Hypertension and cardiovascular risk

Giuliana Valerio, MD, PHD, associate professor of pediatrics at the Parthenope University of Naples, Italy, and one of the study authors, says that the lower blood pressure threshold to classify children and teenagers as hypertensive in the AAP guidelines helped to classify more children and adolescents with high risk factors.

“As a result of the lowered blood pressure cutoffs, the 2017 AAP criteria allowed us to identify more obese children and teenagers with insulin resistance and atherogenic dyslipidemia who would have been missed using the ESH criteria,” she says. “In addition, children and adolescents reclassified as hypertensive by the 2017 AAP criteria, but normotensive by the old criteria, also have higher odds of left ventricular hypertrophy than individuals classified as nonhypertensive by both criteria.”

The plan now is to request ESH to officially update its criteria, noting that having 2 different sets of criteria for hypertension in children is both “confusing and detrimental.” The ability to identify these children and adolescents early and accurately is essential, she adds.

“The association between obesity, abnormal cardiometabolic risk factors, hypertension, and left ventricular hypertrophy represents a threatening cluster in children and adolescents and should not be overlooked because appropriate management can decrease cardiovascular risk,” Valerio says.

Ms Zimlich is a freelance writer in Cleveland, Ohio. She 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.

For reference, go to ContemporaryPediatrics.com/hypertension-and-obesity
Researchers in Canada published a report in the Clinical Journal of the American Society of Nephrology revealing that although the use of hemodialysis to treat patients hospitalized with acute injury has increased, so has the risk for short-term mortality.1

The research team studied 30-day mortality in more than 1300 children hospitalized AKI who received their first dialysis treatment. Data was collected on children aged 29 days to 18 years between 1996 and 2015 in the province of Ontario. The total incidence of children receiving dialysis for AKI was 0.58 per 1000 person years in 1996, but that number rose to 0.65 per 1000 person years by 2015. Over the same period, 30-day mortality rates rose in the cohort, according to the report, jumping from 14% in 1996 to 25% in 2009. Since 2009, however, 30-day mortality has sustained at 20. During the same period, use of peritoneal dialysis in this population has decreased, and the median age at which dialysis initiated dropped from age 13 years in 1996 to age 3 years from 2010 to 2015.

Rahul Chanchlani, MD, MSC, FASN, assistant professor of pediatric nephrology and associate faculty in the department of health research methods, evidence and impact at McMaster Children’s Hospital and McMaster University in Hamilton, Ontario, Canada, led the study and says pediatricians need to take note of the increasing incidence of severe acute injury requiring dialysis in children.

“These high-risk patients need close follow-up, and not just during the hospital stay, but also after discharge, as they are at a higher risk of death,” Chanchlani says.

Pediatricians can help by working to reduce AKIs and the need for dialysis, he adds, offering some advice. “The important ones are avoiding nephrotoxic medications such as nonsteroidal anti-inflammatory drugs and antibiotics, if possible; counseling children and their parents about benefits of adequate hydration and frequent voiding; keeping a close eye on children at high risk of AKI during hospital stay such as preterm babies or those admitted to the intensive care unit; and those with sepsis, shock, cardiac issues, malignancy, or some renal and urological abnormalities,” Chanchlani says. “Any rise in creatinine during the hospital stay should be taken seriously.”

He offered some analysis on the decline of peritoneal dialysis and the reasons behind the increase in hemodialysis as treatment modalities for AKI.

“In our study, there was initially an increase in the 30-day mortality from 14% to 25% until 2009 followed by a decline to around 20% in the more recent years despite an increasing burden of comorbid conditions such as cardiac surgery and mechanical ventilation,” Chanchlani says. “This may be due to various reasons including significant advancement in clinical care of the underlying conditions, better availability of intensive care units, and earlier initiation of dialysis.”

Chanchlani says he was surprised at the rising risk of severe AKI in children over the last 2 decades, as well as the dramatic reduction in the use of peritoneal dialysis for AKI compared with dialysis or continuous renal replacement therapy (CRRT).

“The reasons for the relative decline in peritoneal are significant advances in extracorporeal therapy technology tailored to the pediatric population. This includes the availability of smaller dialyzers permitting the use of smaller extracorporeal volumes, which has made the delivery of hemodialysis and CRRT feasible and safe even in extremely-low-birth-weight babies,” he says. “With the introduction of newer machines for CRRT, it is expected that CRRT utilization will continue to grow.”

Chanchlani says he hopes the study will increase awareness about the problem among pediatricians and stress the need for additional follow-up with high-risk patients.

For reference, go to ContemporaryPediatrics.com/hemodialysis-and-aki

RACHAEL ZIMLICH, RN, BSN

Hemodialysis use in children hospitalized with acute kidney injuries (AKIs) has increased over the last 2 decades, but it is not necessarily improving the outlook for these patients.

More, younger children receive dialysis for acute kidney injuries

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CHILD DEATH

Caring for parents after the sudden death of a child

Pediatricians can use the growing body of knowledge from biomedical and grief research as the basis for improving their care of bereaved parents in crisis.

CHERYL GUTTMAN KRADER

Sudden unexplained death in infants and children is responsible for more deaths than pediatric cancer or heart disease and is the leading cause of postneonatal mortality in most advanced economies throughout the world. There are important questions about increased risks in other children in the family, while bereaved parents often experience severe and prolonged grief that may influence their parenting.

At the American Academy of Pediatrics (AAP) 2019 National Conference and Exhibition in New Orleans, Louisiana, in October, Richard Goldstein, MD, explained the complex needs of families whose children died from sudden infant death syndrome (SIDS) or sudden unexplained death in childhood (SUDC) and discussed the growing body of knowledge from biomedical and grief research as a basis for helping pediatricians provide improved care.

His session titled "Supporting families after the sudden unexpected death of a child" took place on Monday, October 28.

"Pediatricians are very attuned to the importance of giving sleep recommendations for preventing SIDS and are aware of the possible child abuse implications surrounding cases of sudden unexplained death. However, our field has not done as good a job educating clinicians about how to interact with and help families who are in crisis after experiencing the unimaginable," said Goldstein, program director, Robert’s Program on Sudden Unexpected Death in Pediatrics, and assistant professor of Pediatrics, Harvard Medical School, Boston, Massachusetts.

“These are our patients and their families. Sometimes they die following all our advice and, even when they don’t, many of us can feel unprepared about what to say or do,” said Goldstein. “Our educations typically leave us uninformed about strides made by research in this area. It is important that clinicians be prepared to understand and address the concerns of these families beyond just talking about risk factors in the sleep environment.”

Parents almost universally want to know why it happened, how their seemingly healthy child might have died this way, and what it means for their other children. Goldstein heads a program that investigates the possibility of undiagnosed diseases and vulnerabilities in cases of unexplained deaths. He shared research that provides some answers.

Brainstem vulnerability is a driving factor in many cases of SIDS, preventing infants from responding to what is otherwise a modest threat in their sleep environment and leading to a failure to autoresuscitate and arouse. “We have found reduced serotonin in the brainstems of SIDS infants and shown in animal models that this deficiency causes autoresuscitation failure,” said Goldstein.

His group’s SUDC research has found changes in the hippocampus that are otherwise considered hallmarks of...
Related to this discovery, they have discovered a gene present in some SIDS cases linked to Dravet syndrome, a severe epilepsy syndrome.

“Whereas this research is significant and may provide direction for the future, to be a good pediatrician for these families requires an understanding of the psychological crisis they are going through,” said Goldstein, who also discussed his grief research that shows extremely high levels of grief-related symptoms that impede a mother’s function.

“We found that while approximately 10% of older adults experience pathologic grief 1 year after losing their life partner, 60% of mothers who lost a child to SIDS are suffering pathologic grief 1 year later, a burden that continues at high rates for years,” Goldstein points out.

His research has also found ways to identify mothers at higher risk.

Goldstein’s main message was to emphasize the need to remain a family’s pediatrician at an extremely difficult time. He provided practical help for how to reach out to families, help them pursue explanations, and provide needed support.

**COMMENTARY**

The death of a child is an unnatural event, defying life’s natural order. When the death is sudden and unexpected, there can be added trauma for parents, siblings, and extended family members as the entire family dynamic has changed.

At the AAP 2019 National Conference and Exhibition, Richard Goldstein, MD, addressed this important topic in a session titled “Supporting families after the sudden unexpected death of a child.” As Dr. Goldstein highlights, the pediatrician has a unique role to play in meeting the complex medical and psychosocial needs of the family. However, our training has not adequately prepared us for how to support families after these deaths.

When a child dies suddenly and unexpectedly, the family is faced with a multitude of professionals and agencies, including first responders, law enforcement, emergency department providers, child protective services, and medical examiners.

The pediatrician can act as a liaison between these professionals and the family. In providing support for families, it is important for pediatricians to recognize that grief is not linear and that the families’ needs may change over time.

When the child is aged older than 1 year, there is the added challenge that there is limited awareness of the category of death of sudden unexplained death in childhood (SUDC), which is the sudden and unexpected death of a child aged between 1 and 18 years that remains unexplained after a thorough investigation including autopsy. It affects approximately 400 children annually and is the fifth-leading category of death in children aged 1 to 4 years. However, most of the research in sudden death in Pediatrics has focused on infant deaths. As a result of this lack of awareness, pediatricians may be unaware of how to connect families with important resources such as the SUDC Foundation (sudc.org).

In recognition of the need for more consistent investigations and the need for guidance for medical professionals handling these deaths, the SUDC Foundation provided a scientific grant for a collaboration between the AAP and the National Association of Medical Examiners to form consensus guidelines for sudden deaths in Pediatrics titled “Unexplained pediatric deaths: Investigation, certification, and family needs.” These guidelines, which will be published in January 2020 and available online (sudpeds.com), represent an important step in improving care to families affected by sudden pediatric deaths.

The consensus guidelines and Dr. Goldstein’s session are significant steps to addressing the gap in our education around supporting families after pediatric deaths and encouraging pediatricians to remember that their role as the child’s pediatrician should not end with the child’s death.

— Erin Bowen, MD, is a pediatrician in practice in Ansonia, Connecticut. She is a member of the American Academy of Pediatrics (AAP) and a member of the AAP Section on Child Death Review and Prevention. She is also a member of the Sudden Unexplained Death in Childhood (SUDC) Foundation Board of Directors, working on the foundation’s Medical Education Initiatives, with a goal of increasing medical education of SUDC to professionals at the forefront of care for affected families.
ALLERGY AND IMMUNOLOGY

How to manage uncontrolled asthma and its causes

Pediatricians need to implement the strategies of assessing, adjusting, and reviewing symptoms and risks of severe asthma to confirm the diagnosis and implement appropriate interventions.

MARY BETH NIERENGARTEN, MA

In the United States, 8.4% of children have asthma. Among this cohort, 5% have asthma that is classified as severe and poorly controlled despite adherence to standard treatments. However, a much larger proportion of children with asthma report frequent symptoms that are difficult to control. The highest rates of uncontrolled asthma occur in black children (63%), young children aged 0 to 4 years (59%), and girls (53%). A number of factors can affect asthma control in these children and make it difficult to control.

To help pediatricians and front-line healthcare providers recognize and diagnose difficult-to-control asthma in children, Susan S. Laubach, MD, FAAP, associate clinical professor of Pediatrics, University of California San Diego, and director, Allergy Clinic, Rady Children’s Hospital, San Diego, California, provided an overview of factors that make asthma difficult to control and key questions that should be asked to identify these factors to make the diagnosis during a session at the American Academy of Pediatrics (AAP) 2019 National Conference and Exhibition in New Orleans, Louisiana, titled “Breathe easy: Diagnosis and management of difficult-to-control asthma” on Sunday, October 27, 2019.

These key questions include: 1) Is this really asthma?; 2) Are the treatments working?; 3) Are there unrecognized triggers?; and 4) Are there comorbidities? For each question, Laubach used a case study to illustrate how clinicians should approach a child with difficult-to-control asthma to ensure optimal management.

Laubach discussed a personalized asthma management approach taken from the 2019 Global Strategy for Asthma Management and Prevention (GINA) Report that is based on a strategy of assessing, adjusting, and reviewing symptoms and risks of severe asthma to confirm the diagnosis and implement interventions. As the first step, assessing requires confirming a diagnosis if necessary; identifying symptom control and modifiable risk factors as well as comorbidities; inhaler technique and adherence; and understanding patient goals. Adjusting includes treatment of modifiable risk factors and comorbidities; managing with nonpharmaceutical strategies; educating the patients; and use of asthma medications. Reviewing focuses on reviewing the response to treatments including symptoms, exacerbations, adverse effects, lung function, and patient satisfaction.

In addition to a review of the recommended step-up treatments used to control asthma symptoms, Laubach listed other factors that contribute to making asthma difficult to control. Many of these factors, she emphasized, are modifiable. She urged clinicians to consider “other diagnoses in the differential diagnosis of a child who coughs and wheezes; adhering to the treatment guidelines to make sure the correct medications and doses are being used for a child’s level of severity; checking inhaler technique; addressing parental concerns about adverse effects of medications; assessing for environmental triggers (such as allergies, tobacco, smoke exposure, and pollution); comorbidities (such as obesity, reflux, and sinus disease); and age-specific concerns (especially in adolescence).”

Laubach ended her talk with a brief description of new biologic therapies available for older children and adults.

Overall, Laubach emphasized the need for pediatricians to look for factors underlying difficult-to-control asthma and getting help as needed. “When asthma is difficult to control, consider the underlying factors and consider consulting allergy or pulmonary specialists,” she said.

COMMENTARY

Asthma remains the cause of substantial morbidity and even mortality in children and young adults. Discerning the relative
degree of disease severity can be challenging. Although severe, difficult-to-control asthma is distributed asymmetrically across sex (female predominance), socioeconomic strata (uninsured), and race (black children), and children are afflicted irrespective of geography, wealth, or race.

On Sunday, October 27, 2019, Susan S. Laubach MD, associate clinical professor, University of California San Diego, and director, Allergy Clinic, Rady Children’s Hospital, San Diego, California, provided an overview of factors that make asthma difficult to control during a session titled “Breathe easy: Diagnosis and management of difficult-to-control asthma.”

Several aspects of the presentation and difficult-to-control asthma merit comment. First, difficult-to-control asthma may derive from a cause that is addressable. Undertaking a careful history that includes environmental exposures (pollutants, volatile chemicals, dust mites), living situation (smokers, pets, heat source), as well as allergic and family history can inform both diagnosis and treatment. Prolonged exposure to an inflammatory stimulus can lead to chronic inflammation and poorly controlled asthma.

Second, clinicians managing children with difficult-to-control asthma should ensure both compliance and the diagnosis. From a compliance perspective, patients may be in possession of the correct medication, but they are delivering it incorrectly. Review of delivery techniques and capacity for the patient and family to comply with the medications as prescribed is essential. Moreover, considering the difficult-to-control asthma patient from a comprehensive perspective is important as highly labile asthma may result from a cause such as aspiration, allergy, or reflux.

The significance of the difficult-to-control asthma patient is amplified further by the changes unfolding in our environment. With global warming and increasing levels of particulate matter in the air, especially in developing countries and inner cities, there is reason to believe that the prevalence of difficult-to-control asthma will be increasing. Further, the advent of increasingly specific therapeutic tools, more precise and more personal, will allow for the delivery of more bespoke care than ever before. Thus, being able to achieve a highly defined, “thin” phenotype will enable clinicians to mitigate the clinical harm associated with difficult-to-control asthma by providing therapies that address the underlying cause.

—David N. Cornfield, MD, is the Anne T. and Robert M. Bass Professor in Pulmonary Medicine, and director, Center for Excellence in Pulmonary Biology, Department of Pediatrics and (by courtesy) Surgery, Stanford University School of Medicine, Stanford, California.

INFECTION DISEASE

What’s new in the vaccine wars

To address the different fears motivating vaccine-hesitant parents versus antivaccine parents, one must understand the historical resistance to vaccination.

MARY BETH NIERENGARTEN, MA

Resistance to vaccines is not new. Starting with the first vaccine developed in the late 1700s/early 1800s for smallpox through current times, people have resisted vaccines.

“What we are looking at today is not new,” said Paul A. Offit, MD, director of the Vaccine Education Center and attending physician in the Division of Infectious Diseases at Children’s Hospital of Philadelphia, Pennsylvania. “It is historic, but the good news is that I think there is a path forward.”

The path forward he suggests lies in understanding the historical resistance to vaccines and the reasons behind the resistance. Calling this a “war on vaccines,” Offit described a number of issues related to the fight around vaccines such as the whooping cough vaccine and measles/mumps/rubella vaccine. These issues inform what is going on today, he said.

Offit spoke during a session at the American Academy of Pediatrics (AAP) 2019 National Conference and Exhibition in New Orleans, Louisiana, on Sunday, October 27, titled “Communicating the science of vaccines to parents, the public, and the media.” The bulk of his talk centered on the current resistance to vaccines. He underscored 2 groups of people who primarily make up the resistance: vaccine-hesitant parents and antivaccine parents or conspiracy theorists.

Underlying the resistance in both groups, he said, is fear. “People are compelled by fear more than reason,”

“I don’t think people fear the diseases any more, and so they fear other things, such as misconceptions about vaccines.”

—PAUL A. OFFIT, MD
he emphasized. “I don’t think people fear the diseases anymore and so they fear other things, such as misconceptions about vaccines.”

As an example, Offit pointed to the lack of resistance to the polio vaccine despite the real tragedy that occurred in 1955: Using a bad batch of the vaccine, 120,000 children inadvertently were inoculated with a live polio virus that caused short-lived polio in 40,000 children, permanent paralysis in 164, and death in 10. “When you fear the disease more than the vaccine, you are willing to accept the safety issues,” Offit said.

Fear of vaccine-preventable diseases no longer motivates people. “People don’t fear diseases such as flu and human papillomavirus (HPV), but they are wrong not to fear them,” he said, pointing out that the flu has killed more people than all other vaccine-preventable diseases combined.

The fear motivating the 2 groups of people he sees as the main resistors to current vaccines he suggests is different. For the first group, the vaccine-hesitant parents, he emphasized their true hesitancy about the vaccines because they are not as compelled and fearful of the diseases themselves. Social media plays a role in spreading bad information that is quick and easy to access.

Underlying the fear of the antivaccine group, Offit said, is conspiratorial thinking. “They believe there is a conspiracy to hide the truth and that the pharmaceutical industry is behind the conspiracy.”

Although he said that there is little one can do to convince the antivaccine people of the value of vaccines, Offit underscored the need for compassionate and compelling education of the vaccine-hesitant group. “I think information is of value to people who are receptive to information,” he said.

COMMENTARY

Even though resistance to vaccines has been present since the first vaccine was developed in the late 1700s, over the last decade the antivaccine movement has grown exponentially. The proponents have become well organized, very vocal, and brash. They have flooded all forms of media, especially social media and the Internet, with their messages of misinformation about vaccines, distrust, conspiracy theory beliefs, and “fear,” much of which has a major negative impact on many parents seeking information on vaccinating their infants and children.

Additionally, the antivaccine group is incredibly well funded allowing them to continue to engage in their fight. This has all led to a growing number of significant outbreaks of vaccine-preventable diseases.

Dr. Paul Offit’s session “Communicating the science of vaccines to parents, the public, and the media” at the AAP 2019 National Conference provided a very insightful and comprehensive look into the current underlying reasons that drive the antivaccine movement, with “fear” rising to the top as being the most compelling factor leading to vaccine rejection.

Dr. Offit emphasized that people who are antivaccine or vaccine hesitant are compelled by different types of “fear” and that reasoning and logic play a little role in the decision to vaccinate. He pointed out that there is not much that can be done to convince true antivaccine people about the value of vaccines. However, he strongly stressed the need for practitioners to be understanding and provide guidance and education to the vaccine-hesitant group, who, in the vast majority of cases, are receptive to information and ultimately understand the value that vaccines provide.

The runaway train of the antivaccine movement has continued to rapidly gain momentum and we as a society are in grave danger of derailing much of the progress that has been made in the control of vaccine-preventable diseases. We as pediatric healthcare providers need to remain staunch advocates for the value and importance of vaccines. By providing understanding, information, and education, we can slow this movement and provide important protection to our patients.

—Tina Q. Tan, MD, is professor of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, and Infectious Diseases attending, Ann and Robert H. Lurie Children’s Hospital of Chicago, Chicago, Illinois.
Recognize & Refer

Retinoblastoma CONTINUED FROM PAGE 53

in both eyes. If a parent comes in with photographs where one eye is white and one eye is red, and it’s in more than one photograph, it’s something to be aware of. Because people take so many photographs these days using their cell phones, we can therefore know that we need to pay attention to that a little bit more than we used to when we were looking back at old photographs.

Another sign is redness of the eye itself or glaucoma, changes in vision, lazy eye, which is an indication of a change in vision, and then just leukocoria on exam or the physician seeing the lack of the red reflex. Those are all signs that pediatricians should be looking for.

Q. What are the best treatment options for retinoblastoma in children?

A. Children diagnosed with retinoblastoma with very small tumors often can be treated with what we call local therapies, mostly commonly cryotherapy or laser therapy, without needing a removal of the eye, also known as enucleation, or needing chemotherapy or radiation therapy. That’s one of the reasons we are very vigilant about doing exams on children who have a family history, for example, before they develop clinical signs of the disease, to pick up tiny little bits of retinoblastoma early to save them from those therapies.

The other treatments that are increasingly being used are chemotherapy delivered directly to the eye through the ophthalmic artery and then chemotherapy is directed, is infused, directly to the retina. This allows us to avoid systemic chemotherapy, be preserving of vision, can help us avoid removal of the eye, and avoids needing to use external beam radiation therapy.

Another therapy used when external beam radiation therapy is necessary is proton beam radiation, which is increasingly available and used in retinoblastoma patients because it can limit the dose in these very young children, limit the spread of the dosing of radiation outside of the eye. It really can target where the tumor is and avoid dosing areas such as the bones around the eye, because when we do that in very young children, the dose, to the bones around the eye or the soft tissues around the eye, is known to be associated with the development many years later of tumors of that area because of the tumorigenic effect of the radiation. So, if we can limit where we deliver radiation, we can hopefully reduce the risk that those secondary tumors will develop.

Q. Most importantly, at what point should a community pediatrician refer a patient to a specialist?

A. Any child who has a family history suspicious for retinoblastoma—that would be an unknown history of visual losses in multiple family members, a parent who has a glass eye, a parent who says there was something wrong with his/her eye as a baby but didn’t know what it was—those children all should be referred just based on the family history, and that should be done very early in infancy. Pediatricians are very good at looking for red reflex and, obviously, if they see an abnormality on physical exam, that should be referred. If a parent comes in with photographs that are of concern, I think that’s a reason to refer to a specialist as well, and that specialist would be a pediatric ophthalmologist. It’s not necessary to go directly to a pediatric oncologist at that point. I think the diagnosis is mostly made by observation by a pediatric ophthalmologist who has expertise in this field.

Q. Dr. Diller, is there anything else that you would like to add as a final thought for our community of pediatricians?

A. The other thing to remember is that increasingly genetic counselors who have expertise in cancer predisposition syndrome are able to take a family history and assess whether or not a child should be genetically tested for a risk of retinoblastoma. That is something that a pediatrician might consider if there’s a family history that is somehow concerning, and that might be the first level of referral before a pediatric ophthalmologist in certain situations.

Dr. Diller has nothing to disclose.

Dr. Johanek is a staff pharmacist at Southwest General Health Center, Middleburg Heights, Ohio. She 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.
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Focus on retinoblastoma

This month’s spotlight is Pediatric Oncology as Contemporary Pediatrics sits down exclusively with pediatric oncologist Lisa Diller, MD, vice chair, Clinical Affairs, and medical director, Clinical Cancer and Blood Disorders Service Line, Dana-Farber Cancer Institute, Boston, Massachusetts, to discuss the one key condition for which she believes community pediatricians should be especially aware—retinoblastoma.

ERIN JOHANEK, PHARMD

Q. Dr. Diller, can you tell us why you think that retinoblastoma is something of particular concern for pediatricians?

A. Retinoblastoma is important for pediatricians because early detection can make a huge difference in terms of the outcome for the child. Knowing who might be at risk for retinoblastoma or what signs and symptoms are important to pick up for retinoblastoma is very important because the pediatrician is usually the first person to see the patient who might have retinoblastoma.

Q. What are the underlying reasons for maybe the increased severity of retinoblastoma in children?

A. It’s not really increased severity that I’m thinking about. I’m thinking about the possibility of picking up a retinoblastoma early that makes a huge difference. So, the severity of retinoblastoma in terms of the aggressiveness of the treatment is often related to delays in diagnosis, and if we can find retinoblastomas early and get the children into treatment, we can often avoid therapies that can have long-term effects for the rest of a child’s life, such as radiation therapy or losing an eye. That’s what I think it’s important for pediatricians to know.

Q. What advice can you offer as far as those diagnostic clues that the pediatrician should be on the lookout for to properly identify retinoblastoma?

A. First of all, retinoblastoma can run in families, so it’s very important to have a good family history. Often adult parents who had retinoblastoma may not be aware of the word retinoblastoma because they were treated at a very young age. They may have had an eye removed as a young child for reasons that they don’t know. They’ve had a glass eye their whole lives or a false eye their whole lives and they may not know this. So, unless the pediatrician is aware of the parent’s history he or she might be missing a clue. I had a recent patient, for example, whose mother lost an eye as a baby, was never told why, and then her child was diagnosed with retinoblastoma but she was completely unaware of the relationship between her likely retinoblastoma and what happened to her child.

Another sign or symptom that a pediatrician should be aware of—and that we’re seeing at increased frequency because people take so many photographs—is the lack of red reflex that you normally see in a photograph. In a photograph, when you shine a light, use the flash, you often see the reflection of the retina.

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