CONTEMPORARY Pediatrics®

BACK TO SCHOOL AND MORE

AUGUST 2013
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Expert Clinical Advice for Today's Pediatrician

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Neurologic complications of influenza

HEAD LICE
Myths, facts, treatments

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Available in Pharmacies

Quillivant XR™ (methylphenidate HCl) is the first and only extended-release methylphenidate oral suspension for ADHD treatment

Quillivant XR™ (methylphenidate HCl) CII demonstrated efficacy at its primary endpoint of 4 hours and at all time points measured from 45 minutes to 12 hours post-dosing.

Quillivant XR contains approximately **20%** immediate-release and **80%** extended-release methylphenidate, which contributes to its pharmacokinetic profile characterized by a rapid initial absorption followed by a continuous release of methylphenidate.

INDICATION

Quillivant XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Quillivant XR was established in a 2-week, placebo-controlled trial in children aged 6 to 12 years with a diagnosis of ADHD. Accumulated efficacy data from other methylphenidate products were also considered.

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including Quillivant XR, 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.

- Quillivant XR is contraindicated:
  - In patients known to be hypersensitive to methylphenidate or other components of Quillivant XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported.
  - During treatment with monoamine oxidase inhibitors (MAOIs), and also within 14 days following discontinuation of treatment with an MAOI because of the risk of hypertensive crisis.
- Stroke and myocardial infarction have occurred in adults treated with CNS stimulants at recommended doses. Sudden death has occurred in children and adolescents with structural cardiac abnormalities and other serious cardiac problems, and in adults taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with Quillivant XR.
- CNS stimulants cause an increase in blood pressure (mean increase approximately 2-4 mm Hg) and heart rate (mean increase approximately 3-6 bpm). Some individuals may have larger increases. Monitor all patients for hypertension and tachycardia.
- Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to Quillivant XR use.
- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Growth should be monitored during treatment with stimulants, including Quillivant XR. Patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

The Quillivant XR $20 Co-pay Card* may help eligible patients save up to $1200 per year!

*Terms and Conditions apply. Please see full Terms and Conditions at www.QuillivantXRPro.com/Terms-and-Conditions. **This co-pay card is not health insurance. The co-pay card is only accepted at participating pharmacies.** For any questions, please call 1-800-932-4371, or write: Pfizer, ATTN: Quillivant XR, PO Box 2249, Morrisville, PA 19067-8049. **No membership fees required.** Savings limited to $100 per 30 days for up to 12 uses within the program term. Card may be used once every 30 days. The maximum limit is $1200 per year or the amount of the co-pay you paid, whichever is less.

IMPORTANT SAFETY INFORMATION (cont'd)

- Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) expected adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased. There is limited experience with Quillivant XR in controlled trials. Based on this limited experience, the adverse reaction profile of Quillivant XR appears similar to other methylphenidate extended-release products. 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 (aged 6-12 years) were affect lability (9%), excoriation (4%), initial insomnia (2%), tic (2%), decreased appetite (2%), vomiting (2%), motion sickness (2%), eye pain (2%), and rash (2%).
- Based on animal data, use of Quillivant XR during pregnancy may cause fetal harm. Quillivant XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing mothers should be advised to discontinue drug or discontinue nursing, taking into consideration the importance of the drug to the mother.

For more information, please visit www.QuillivantXRPro.com

Quillivant XR™ (II)
methylphenidate HCl
for extended-release oral suspension
25 mg/5 mL

*Please see Brief Summary of Prescribing Information, including **BOXED WARNING** regarding Abuse and Dependence, on the following page.*

Pfizer

Quillivant XR™ (methylphenidate HCl) for extended-release oral suspension, CII Rx only
BRIEF SUMMARY: Consult Full Prescribing Information for Complete Product Information.

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including Quillivant XR, 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 *[see Warnings and Precautions, Drug Abuse and Dependence].*

INDICATIONS AND USAGE

Quillivant XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Quillivant XR was established in a 2-week, placebo-controlled, laboratory classroom, crossover study in children aged 6-12 years with a diagnosis of ADHD. Patients in the trial met DSM-IV-TR® criteria for ADHD. Accumulated efficacy data from other methylphenidate products were also considered.

CONTRAINDICATIONS

Hypersensitivity to Methylphenidate or other Components of Quillivant XR. Quillivant XR is contraindicated in patients known to be hypersensitive to methylphenidate, or other components of Quillivant XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products.

Monoamine Oxidase Inhibitors Quillivant XR is contraindicated during treatment with monoamine oxidase inhibitors, and also within 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (MAOI), because of the risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS

Potential for Abuse and Dependence CNS stimulants, including Quillivant XR, 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 [*see Drug Abuse and Dependence*].

Serious Cardiovascular Reactions Stroke and myocardial infarction have occurred in adults treated with CNS stimulants at recommended doses. Sudden death has occurred in children and adolescents with structural cardiac abnormalities and other serious cardiac problems, and in adults taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with Quillivant XR.

Blood Pressure and Heart Rate Increases CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients 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 pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing Quillivant XR. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0 in placebo-treated patients.

Long-Term Suppression of Growth CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including Quillivant XR. Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or nonmedication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated children 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 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. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth; however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

ADVERSE REACTIONS

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in 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, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia. *Clinical Trials Experience with Quillivant XR in Children and Adolescents with ADHD*. There is limited experience with Quillivant XR in controlled trials. Based on this limited experience, the adverse reaction profile of Quillivant XR appears similar to other methylphenidate extended-release products. 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 6-12 years) were affect lability, excoriation, initial insomnia, tic, decreased appetite, vomiting, motion sickness, eye pain, and rash.

Table 2. Common Adverse Reactions occurring in ≥2% of subjects on Quillivant XR and greater than placebo during the controlled cross-over phase

Adverse reaction	Quillivant XR (N=45)	Placebo (N=45)
Affect lability	9%	2%
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%
Rash	2%	0%

Postmarketing Experience The following adverse reactions have been identified during post approval 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. These adverse reactions are as follows:

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura
Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystole, Supraventricular tachycardia, Ventricular extrasystole
*Eye Disorder*s: Diplopia, Mydriasis, Visual impairment
General Disorders: Chest pain, Chest discomfort, Hyperpyrexia
Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative 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
Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia
Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Mania
Urogenital System: Priapism
Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema
Vascular Disorders: Raynaud's phenomenon

DRUG INTERACTIONS

MAO Inhibitors Do not administer Quillivant XR concomitantly with monoamine oxidase inhibitors 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.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C Risk Summary There are no adequate or well-controlled studies with Quillivant XR in pregnant women. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in mothers dependent on other stimulant products such as amphetamines. Methylphenidate showed some potential for teratogenicity when pregnant animals were treated during organogenesis: an increased incidence of fetal spina bifida in rabbits at 40 times the maximum recommended human dose (MRHD), on a mg/m^2 basis, and an increased incidence of fetal skeletal variations in rats at 7 times the MRHD. A decrease in body weight gain was seen in the offspring of rats treated with methylphenidate throughout pregnancy and lactation at 4 times the MRHD. Quillivant XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Clinical Considerations Stimulant medications, such as Quillivant XR, cause vasoconstriction and thereby decrease placental perfusion. Infants born to amphetamine dependent mothers have an increased risk of premature delivery and low birth weight. Monitor infants for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness. Animal 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 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 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 (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mg/m^2 basis), but no other effects on postnatal

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Quillivant XR™ (methylphenidate HCl) Brief Summary continued...
development were observed. The no effect level for pre- and postnatal development in rats was 15 mg/kg/day (equal to the MRHD on a mg/m^2 basis). **Nursing Mothers** Methylphenidate is present in human milk. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of Quillivant XR have been established in pediatric patients ages 6 to 17 years. Use of Quillivant XR in pediatric patients 6 to 12 years of age is supported by adequate and well-controlled studies. Use in 12 to 17 year olds is supported by the adequate and well-controlled studies of Quillivant XR in younger pediatric patients and additional pharmacokinetic data in adolescents, along with safety information from other methylphenidate-containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established. Safety and efficacy in pediatric patients below the age of 6 years have not been established. Long Term Suppression of Growth Growth should be monitored during treatment with stimulants, including Quillivant XR. Children who are not growing or gaining weight as expected may need to have their treatment interrupted [*see Warnings and Precautions*]. Juvenile Animal Data Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in 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 6 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. In the study conducted in young rats, methylphenidate was 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 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (12 times the MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown. **Geriatric Use** Quillivant XR has not been studied in patients over the age of 65 years.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Quillivant XR contains methylphenidate, a Schedule II controlled substance.
Abuse CNS stimulants including Quillivant XR, 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. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which can result in overdose and death [*see Overdosage*]. To reduce the abuse of CNS stimulants including Quillivant XR, 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 Quillivant XR use.
Dependence Tolerance 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 Quillivant XR. 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 Quillivant XR. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include extreme fatigue and depression.

OVERDOSAGE
Signs and Symptoms Signs and symptoms of acute methylphenidate overdosage, 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, and dryness of mucous membranes.
Management of Overdose Consult with a Certified Poison Control Center for up-to-date guidance and advice on the management of overdosage with methylphenidate (1-800-222-1222.) Provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosage. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

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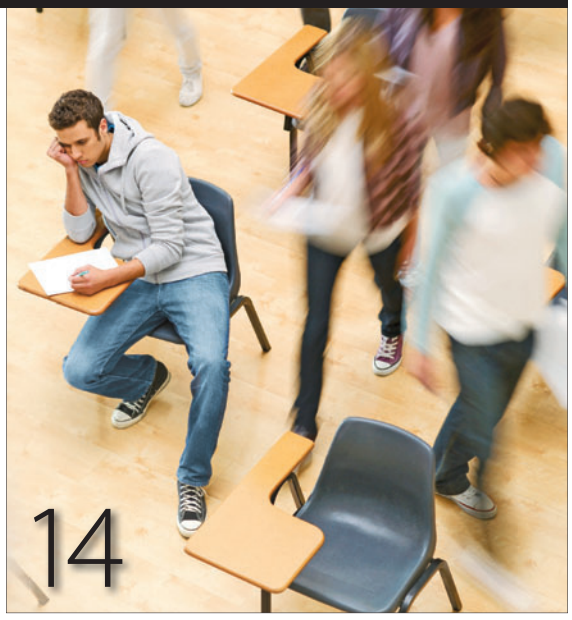

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WHEN ADHD MEDICATIONS PRESENT A NUTRITIONAL CHALLENGE, CONSIDER A NUTRITIOUS SOLUTION.

Stimulant ADHD medications can suppress a child's appetite, leading to weight loss and delayed growth.[1-4]

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*PediaSure SideKicks 35% less calories (150) vs PediaSure base (240 calories) and 40% less fat (5 g) vs PediaSure base (9 g) per 8 fl oz serving.

References: 1. Wigal T, Greenhill L, Chuang S, et al. Safety and tolerability of methylphenidate in preschool children with ADHD. *J Am Acad Child Adolesc Psychiatry.* 2006;45:1294-1303. **2.** Swanson J, Greenhill L, Wigal T, et al. Stimulant-related reductions of growth rates in the PATS. *J Am Acad Child Adolesc Psychiatry.* 2006;45:1304-1313. **3.** Faraone SV, Biederman J, Monuteaux M, Spencer T. Long-term effects of extended-release mixed amphetamine salts treatment of attention-deficit/hyperactivity disorder on growth. *J Child Adolesc Psychopharmacol.* 2005;15:191-202. **4.** Zachor DA, Roberts AW, Hodgens JB, Isaacs JS, Merrick J. Effects of long-term psychostimulant medication on growth of children with ADHD. *Res Dev Disabil.* 2006;27:162-174.

Abbott Nutrition

PEDRO A PIEDRA, MD

WHY VACCINATE SCHOOL-AGED CHILDREN AGAINST INFLUENZA?

Many people consider influenza a nuisance that comes every winter. It is part of the normal cycle of colds that begins after school starts, causing havoc and disruption in the routine activities of family living. What people do not know, or have forgotten, are the following facts about influenza and influenza vaccines.

- Every year, an influenza epidemic strikes the United States, infecting 5% to 20% of the population. Preschoolers and school-aged children are the age groups most likely to be infected with influenza.
- Influenza causes more hospitalizations and deaths in children and adults than any other vaccine-preventable disease in the United States. In the 2012-2013 season, more than 150 children were documented to have died from influenza; many of them were healthy and not vaccinated against influenza.
- Many more children die from influenza each year but go unrecognized. The Centers for Disease Control and Prevention estimated that 1,280 children died during the 2009 H1N1 pandemic; only 348 children were reported to have died from laboratory-confirmed influenza.
- Influenza vaccines are safe and provide a good level of protection against influenza.
- There are 2 types of influenza vaccines approved for use in US children: the live attenuated influenza vaccine (LAIV) that is approved for healthy children aged 2 through 17 years; and the inactivated influenza vaccine (IIV) that is approved for children aged 6 months through 17 years and with at-risk conditions.
- Quadrivalent influenza vaccines will make their debuts in 2013-2014. These vaccines contain vaccine strains for both influenza A subtypes (H3N2 and H1N1pdm09) and both influenza B lineages (B-Yamagata and B-Victoria). The quadrivalent vaccines will provide broader coverage compared with the standard trivalent formulation that contains vaccine strains for both influenza A subtypes and only 1 influenza B lineage.
- Improving influenza vaccination coverage in children can reduce influenza illness in family members and other susceptible persons in the community. This concept is called indirect or herd protection.

DR PIEDRA is professor of Molecular Virology and Microbiology, and Pediatrics, Baylor College of Medicine, Houston, Texas, and director, Viral Diagnostic Laboratory, Houston. He has been principal investigator for clinical trials studying viral infections, immunology, and vaccine safety. He is also a physician at Texas Children's Hospital, Houston.

A national wake-up call

The burden of influenza in children was unrecognized for many years.[1] The substantial number of influenza-associated deaths among US children in the 2003-2004 season brought attention to the severity of influenza in healthy children. Sixty-seven percent of the 153 children who died from influenza that year did not have an at-risk medical condition recognized by the Advisory Committee on Immunization Practices (ACIP) for receiving influenza vaccine. Thirty-seven percent of the children who died were aged older than 5 years.[2]

Infants and children are highly susceptible to influenza because they either have not been infected or have been infected less often with 1 of the major circulating influenza viruses (H1N1, H3N2, B-Yamagata-like, or B-Victoria-like) compared with adults. School-aged children also experience high rates of influenza infection, febrile illness, and school absenteeism. During an outbreak, 63 school days were missed for every 100 children.[3] An increase in work-related absenteeism also occurred among

TO READ MORE on this topic by Dr Piedra, go to ContemporaryPediatrics.com/flu_vaccine_in_children

the parents who missed approximately 1 day of work for every 3 days of school missed by their children.

Influenza causes secondary bacterial pneumonia and serious disease associated with organ systems other than the respiratory tract. Hospitalization due to acute febrile illness and central nervous system disease adds to the spectrum of serious disease in children attributed to influenza. Influenza in children also exerts a significant direct and indirect financial cost. Only in the last decade has ACIP appreciated the burden of influenza in children; it now recommends influenza vaccine for all children aged 6 months and older.[4]

Children are frequently cited as the major vector for the transmission of influenza virus within families, schools, and communities because children have high infection rates, prolonged viral shedding with large amounts of infectious virus, and come in close contact with susceptible classmates. Models suggest that the likelihood of an individual becoming infected with influenza increases 2-fold if the household includes a member aged younger than 18 years compared with those without children.[5]

"Herd protection" works

Monto and colleagues were some of the first to recognize that children played an important role in the dissemination of influenza virus.[6] In a proof-of-concept study, 86% of school-aged children residing in a small community were vaccinated with a single dose of IIV in 1968. A significant overall reduction in influenza-associated illnesses was observed in the intervention community.

Our experience in central Texas suggests that vaccination coverage as low as 20% to 25% in children, primarily with the LAIV delivered by nasal spray, can significantly reduce medically attended acute respiratory illness (MAARI) in adults.[7]

In Ontario, Canada, the high-risk-based influenza immunization program was expanded to a universal influenza immunization program in October 2000.[8,9] In the United States, a universal influenza immunization recommendation for children was made in 2008 and expanded to all persons aged 6 months and older in 2010.[4,10]

Universal influenza vaccination has the potential to substantially reduce overall morbidity, mortality, and health care cost related to influenza. To achieve a substantial impact, high vaccination coverage is needed. Preliminary estimates for influenza vaccination coverage in 2012-2013 were about 55% for all children and about 35% for all adults.[11]

The medical home has been the primary site for administering influenza vaccines to children; however, many children do not have a medical home. Complementing strategies and equitable reimbursement to improve influenza vaccination coverage among all children in the community are needed. A school-based vaccination program is 1 such strategy that can enhance access to vaccines and complement the influenza vaccination program administered at the health care practices. CP

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EDUCATING PARENTS ABOUT VACCINE SCHEDULING IS FAILING

I am disappointed to see yet another editorial statement that suggests we can eliminate the alternative schedule vaccine issue merely by educating our patients better (Brady M. Alternative vaccine schedules are not safer and should be obsolete. *Contemp Pediatr*. 2013;30(6):4-5).

I would posit that pediatricians are already providing adequate education to parents . . . and that simply educating parents is not sufficient. Those of us who are doing this on a daily basis would consider Dr. Brady's suggestions to be naïve. Dr. Brady does not distinguish between the different types of vaccine refusing/alternative schedule people. While I have not seen the following categories published in a formal study of the issue, my descriptions will be readily recognizable to anyone who attempts to counsel parents about vaccines.

1. *The Worried Well*. These are people who . . . really do want to vaccinate, but they have read articles/seen on the Internet/heard from family or friends that vaccines may pose some vague sort of harm. Often, this is related to overwhelming the immune system or that somehow all vaccines cause autism. This group is the largest and is readily reassured by information.

2. *Alternative Schedule*. They often come in asking if I am familiar with "the" alternative schedule. . . . Some of these people may be reassured by information and, in that respect, are similar to group 1. Some come in with their own schedule already printed and ask if this is "OK." . . . Sometimes, after seeing that the first few vaccines haven't harmed their child, they will consent to more vaccines at a time. However, this consent is related to their own direct observations and not to any counseling that I have provided.

3. *Die-hard Refuseniks*. They have done their "research," made their conclusions, and are not interested in being counseled. They view provision of vaccines as a belief system, not as a scientific decision. They generally do not change their views.

4. *Refusers* of most medical interventions, including vaccines. . . . Fortunately, [they are] few in number.

Group 1 is not a problem. They are asking for information, just like they would for side effects of amoxicillin. . . . They are easy, and this group, only, is the group reachable by Dr. Brady's suggestions. Group 4 is reachable by no one and is, fortunately, the rarest. Groups 2 and 3 are the ones who are dangerous to their children and dangerous to society and who are not reached by education. . . . [T]heir decision about vaccines is based on an emotional response to the perceived risk of harm from vaccines, weighed against the intangible risk of diseases they have never seen. To suggest that mere provision of facts and education will change their decision is incorrect and does not account for the emotional response, fear, that these people have. . . .

The simple answer is that if simply educating patients about vaccines were sufficient, then we would not have a problem in the first place. The fact that this editorial is necessary points to the proposed solution being ineffective. Continued focus on getting pediatricians to provide better education to parents is doomed to fail.

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PEDIATRIC POLICIES WILL DEFEAT ALTERNATE VACCINE SCHEDULES

I take strong issue with your recent editorial article by Michael Brady, MD, titled "Alternate vaccine schedules are not safer and should be obsolete" (*Contemp Pediatr*. 2013;30(6):4-5), but perhaps not for the reasons you expect.

What's my beef? My concern is that Dr. Brady inadvertently gave "alternate vaccine schedules" much more respect than they ever, ever deserved by implying that there was once a time that they were not obsolete. Just as a $3 bill never was legal currency in

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Reference: 1. Institute of Medicine Report Brief. Dietary reference intakes for calcium and vitamin D. http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/DRI-Values.aspx. Accessed March 28, 2013.

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the United States, any vaccine schedule not from the ACIP/CDC should have been labeled illegitimate from the moment of its conception. . . . This most especially includes those schedules promoted and sold to parents by Robert Sears, MD, FAAP, and Jay Gordon, MD, FAAP.[1-3] Sears has schedules that tell parents to delay and skip vaccines, and Gordon openly recommends not giving infants any vaccines until they are at least 6 months of age. In my opinion, as a practicing pediatrician, the schedules promoted by these 2 board-certified FAAP pediatricians constitute medical malpractice by these licensed doctors.

As vaccination rates continue to fall in the United States, I have been deeply disappointed by the lack of any public denouncement by pediatric groups (and pediatric publications as well) of these alternate schedules . . . . [W]eekly, parents come to my pediatric practice demanding I vaccinate their children based on the alternate schedules . . . . Sadly, I don't have any direct, by-name, statement-of-fact refutation of these schedules by any professional organization, including the AAP, AAFP, or CDC. . . . Most notable is the complete lack of any policy statements or parent handouts that tell parents clearly and in no uncertain terms that the schedules of Sears and Gordon should never be followed. (The Offit and Moser article, "The problem with Dr Bob's alternate vaccine schedule,"[4] was not written for parents . . . .)

A recent poll of Washington-[State] pediatricians show[ed] that over 77% of them are regularly asked by parents to use alternate vaccine schedules.[5] Even more worrisome, a recent article found that 1 in 10 parents of young children are using alternate vaccine schedules.[6] Also alarming is recently published research showing that alternate vaccine schedules have directly caused a large part of the recent decrease in vaccination rates in a large metropolitan area.[7] Finally, this lack of denouncement is critical because a recent abstract has shown what many of us in primary care have suspected for the last decade: ". . . [T]he variable most predictive of parents' vaccination decisions was the percent of parents' people networks recommending nonconformity."[8]

. . . [S]o far, all the help I've received from those living in the higher echelons of pediatric medicine is to be told to talk longer and harder to parents who are vaccine hesitant. Well, I hate to break the news, but that isn't working . . . and I really need some help from someone bigger than me (such as the AAP, the AAFP, or the CDC). If, as physicians, we can't all agree that such gross and reckless medical misdirection by our own colleagues is not worthy of our group professional criticism, then why bother having professional physician organizations at all?

It is my hope that physician groups grappling with vaccination fears by parents will realize they must join and help us primary care physicians "in the trenches" to convince parents that the only right thing to do is vaccinate their children according to the ACIP/CDC schedule. Silent tolerance of physicians who advocate deviation from that schedule is not an option anymore. If we are to stem the rising tide of vaccine-preventable disease outbreaks in the United States, we must call out those antivaccinationists in our ranks who are trying to "hide in the herd" of the vast majority of pediatricians who do vaccinate by the ACIP/CDC schedule. There should be no herd immunity for Drs. Sears and Gordon.

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IOM forum promotes disaster preparedness specifically for children and their families

KATHRYN FOXHALL

With so many disasters in the last few months, from tornadoes to the Boston terrorist attack, it's time to seize the moment to advocate for preparedness for children and families, argued a number of speakers at a June Institute of Medicine (IOM) workshop on the issue.

"I have never seen so much government buy-in to the concept that children need to be protected as we currently have today," said Irwin Redlener, MD, director of the National Center for Disaster Preparedness at Columbia University and key expert on children and disasters.

Redlener said that after Hurricane Katrina hospitals should have learned to protect generators, not only moving them to a higher floor, but also protecting the fuel supply and the electrical systems. Instead, he said, after Hurricane Sandy, the nation saw pictures of people carrying premature infants down a dark hospital stairwell, a situation that could have been catastrophic.

Additionally, hundreds of Oklahoma schools are without adequate tornado protection, he said. He further questioned the adequacy of evacuation protocols, following the incident in which Oklahoma residents were killed in a traffic jam as they tried to outrun a tornado on the advice of a television weatherman.

Redlener warned that it takes a long time to recover from a disaster. People take far longer to recover than the infrastructure does, and protecting kids from the psychological trauma of big events requires an adult to buffer them. The nation needs to learn to cope with the "resilience erosion," he cautioned, as Mom or Dad may become degraded in their ability to be a safety net after months or years of waiting for things to get better.

Even after all the disasters the nation has had, he said, there still is no central coordinator to manage state, federal, and nonprofit assets and to deal with sometimes uncooperative banks and insurance companies during recovery. Such a coordinator is exactly what families need, he said.

Redlener also warned that although he is a "big believer" in community-based models for pediatric preparedness, those programs are hardly ever scaled up and are not an alternative to what the federal government needs to do with the "largesse of our tax dollars."

Scott Needle, MD, a community pediatrician with the Healthcare Network of Southwest Florida, argued that office-based providers, including pediatricians, have been neglected in organizing for disaster. He told the workshop attendees that there are major disincentives for pediatricians to prepare before a disaster or to get out of their offices and help during a disaster. Medicaid in general, he said, is a low payer and getting enhanced payments requires getting agreement from host authorities on the state and federal levels.

Esther Chernak, MD, MPH, of the Drexel University School of Public Health, cited a study that she worked on for the Pennsylvania Department of Health that found that most pediatricians in the state have little understanding of the public health systems, how they are organized, or their capacity. The study found that many pediatricians do not have the time to think about preparedness planning. They do, however, care about continuity of operations.

According to Chernak, the study showed that most pediatricians wanted information rather than financial aid: real-time situational awareness and pediatric-specific information. They want to get information at least 5 to 10 minutes before the public does so that when people call they can speak knowledgeably about the issues, she said.

On the other hand, Chernak said, health departments often fail to recognize pediatricians' potential to assist in disaster communications to the public, but the departments often overestimate outpatient practices' surge capacity, even for something such as taking phone calls.

Audio and slides of the conference are available at http://iom.edu/Activities/PublicHealth/MedPrep/2013-JUN-10.aspx. CP

ENSURING COLLEGE SUCCESS FOR STUDENTS WITH ADHD

PATRICIA O QUINN, MD

Before adolescents with attention-deficit/hyperactivity disorder (ADHD) head off to college and away from home, many for the first time, their pediatricians need to initiate frank discussions about how ADHD will affect these patients both academically and in their daily living and to help them plan a successful transition to what lies ahead.

According to those who track college graduation rates in the United States, there is a 50% to 60% chance that a college-bound adolescent will not have a successful college experience; in other words, a significant number of students are at risk for leaving college before they graduate.[1] Although individuals with attention-deficit/hyperactivity disorder (ADHD) are less likely than others to attend college, an increase in the number of college students with ADHD has been observed in recent years.[2] Because ADHD frequently has an adverse impact on a teenager's academic, social, and psychological functioning, there is reason to expect that those with ADHD might have problems adapting when they enter into college life. This, in turn, can lead to higher college dropout rates among students with ADHD than among those without the disorder.[3]

When asked about their transition to college, most students with ADHD report it to be "somewhat to very challenging."[4] Only a small percentage of students with ADHD rate the transition as "not very challenging," but this group credits the rigorous demands of their high schools and the opportunities in high school to practice advocating for themselves as the reasons for their success. Students with ADHD often find the transition to college difficult because they were not prepared to advocate for themselves and to meet the increased academic expectations at college. In addition, they report that they have trouble accepting their differences/disability and fulfilling the many demands of the college experience.[4]

Given the growing cost of college and the serious economic problems facing many families, these aborted college experiences create a significant financial burden, not to mention an emotional toll, on both students and parents. Parents are now insisting that students maximize the educational opportunities made possible by their financial sacrifice. Students from families who

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are struggling to make tuition payments cannot afford the luxury of reduced course loads or taking additional semesters to graduate. Some colleges are now setting firmer time limits on how long a student may take to complete a degree. Instead of encouraging the 5-year plan that a number of students have adopted, some colleges are pushing for the 4-year, 8-semester plan, an approach not allowing for as many stops and starts as in the past. Teenagers with ADHD will need to acclimate more quickly and be successful from the beginning or run the risk of being unable to graduate within these new, tighter parameters.[5]

Why is successfully completing college such a problem in the first place? Ironically, adolescents' specific high school experiences may contribute to the difficulty. Most teenagers today lead structured lives and get very little practice making decisions about how to manage their time and life in general. The typical adolescent attends school every day from around 7:30 AM to 3:30 PM, participates in some activity such as a club or sport before dinner, eats dinner, and then may engage in other structured activities or complete homework. Most teenagers have well-meaning parents who have established rules for what needs to happen when. The protectiveness and anxiety of these parents may have led them at times to take over their child's responsibilities and make things happen in an effort to have their teenager avoid stress and failure. In addition, the secondary education system itself may have become part of the problem. Daily assignments, weekly tests, manageable reading assignments, few independent long-range assignments, and teachers who may encourage, direct, control, remind, prod, and sometimes even nag their students to perform all foster dependence. It is, therefore, not surprising that succeeding on their own at college is so challenging for adolescents.

Transition planning, however, can make a big difference in helping teenagers with ADHD be ready for what lies ahead in college. The treating pediatrician can play a significant role in assisting patients with ADHD to ensure that this transition goes smoothly. So, how can this be accomplished? Several factors are beneficial to the transition process. These include: helping students with ADHD gain knowledge about ADHD and how it will affect them at college, helping them develop self-management/self-determination skills, and encouraging them to use the college's resources.

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How ADHD affects students at the college level

Gaining a fuller understanding of ADHD and its ramifications are important factors in its successful management. Although the parents of patients with ADHD may have pursued this information for their children in the past, as young adults their children will need to take responsibility for their disorder and find out as much as they can. By having a detailed discussion with their teenaged patients on how ADHD can affect them at college and what they can do about it, pediatricians can help these patients take the first steps on the road to success. With this goal in mind, it is useful to discuss the following areas with teenaged patients with ADHD. Some books that cover these topics have been included in an additional reading list (see "Additional resources," page 16).

Daily living. The transition from attending high school and living at home to starting college or university studies while living away from home is among the most challenging of transitions for many students; however, it is especially challenging for young adults with ADHD. Parents of a student with ADHD typically provide considerable support for their son or daughter throughout that child's adolescence—including daily reminders about taking medication; frequent prompts to get to bed on time, get up on time, and plan work schedules; and to stay on top of studies.[6] When parents drive away after dropping their son or daughter off at

ADDITIONAL RESOURCES

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college, they take their organizational skills with them and leave their child completely on his/her own, sometimes for the first time. Although many students with ADHD may relish this initial taste of freedom, many quickly find themselves floundering and experience great difficulty managing their daily routines.

Adolescents with ADHD need to be encouraged to spend the time they have left before going off to college to work on these areas. Sometimes that means helping their parents see the benefits of letting go and thus allowing their teenagers to learn to function on their own. This is where the pediatrician may play a pivotal role.

Academic differences. Students with ADHD have little to no experience in handling the more difficult coursework and the freedom and responsibilities they will encounter at college. College is dramatically different from high school, with no adults to prod a teenager and help structure his or her life. Academic expectations are more challenging than those in high school. These differences are at odds with the core symptoms seen in students with ADHD, particularly poor executive functioning, which affects both time management and organizational skills. College students face unlimited possibilities for how to spend their time, and may experience increased academic demands that most have not had in high school, even if they have taken advanced placement classes. Add to this mix an irregular class schedule, professors who do not take attendance or assign and grade daily homework, only a few tests during the semester that cover hundreds of pages of reading, and complex long-term assignments that the student must have the self-discipline to complete. By highlighting the need for good executive functioning skills at college, the pediatrician can call attention to an area that has been found to be critical to academic success. In advising these young patients with ADHD, the idea of working with a coach or academic or peer tutor can also be suggested, emphasizing how such personal support can help them achieve their goals.

For some very bright students with ADHD, high school may not have been a challenge. As a result, they may have been able to excel without much sustained effort. These students will inevitably discover that their last-minute approach to preparing for tests or writing papers will not work at college. In this setting, some will become confused and depressed. In addition to lacking the important time management and study skills needed at college, these students have no experience needing or asking for help. They often view these first academic problems as a sign of personal failure and end up in a cycle of hiding their mistakes from family members and friends. They may work more diligently, but still fail to achieve, regardless of degree of effort. If an adolescent's pediatrician knows this to be the case, the physician can help the patient avert this situation by pointing out how different college is from high school, how the student's ADHD will affect him or her, and encouraging the use of campus resources when needed.

Encouraging use of resources and fostering self-knowledge

Only one-third of college students who received special education services in high school seek such formal accommodations in college. Many of these students do not use all the resources available to them, according to a report from the National Longitudinal Transition Study.[7] Another study also has shown that students with disabilities can graduate at the same rate as their nondisabled peers if they access

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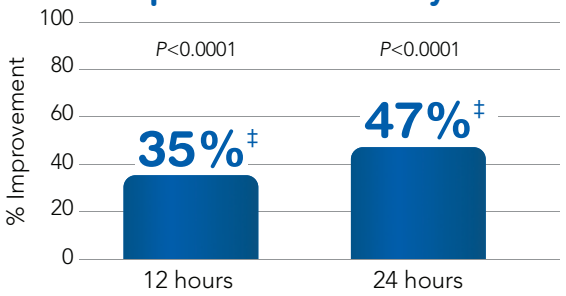

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References: 1. Data on file. **2.** Brown WM, Berg JE, Li Q, Kohut BE. A clinical study to evaluate the efficacy of two marketed zinc oxide-based diaper rash ointments in children with diaper dermatitis. Poster presented at: Clinical Dermatology Conference; October 6-9, 2006; Las Vegas, NV. **3.** Product monograph. 68 FR 33377, June 4, 2003.

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support.[8] Many adolescents with ADHD understand the value of a college education in terms of increased income, cultural and family enrichment, and even better health as life progresses.[9] Most, however, are unaware that they might need to self-disclose their disability and ask for the appropriate resources to be able to graduate on time. By having a discussion that includes questions about each patient's strengths and weaknesses, preferred learning style, passions, and hopes for the future, pediatricians can help these students assess their capabilities and ascertain where they will need support. This self-knowledge is often the first step to self-advocacy.

In addition, pediatricians can encourage their patients with ADHD to:

- **Investigate specialized help on campus.** Specialized services provide support for basic writing and study skills. In addition, tutors may be available to assist with content in various subjects.
- **Access academic accommodations.** If the college they have chosen has a well-established disabilities program, and the staff is aware of and has sensitized the faculty to the needs of students with ADHD, students should have little trouble receiving appropriate accommodations.
- **Consider ADHD coaching.** Difficulties with time management and planning often interfere with the best intentions of college students with ADHD. As a result of the problems they have with setting and achieving their goals, overall daily living tasks and academic achievement may suffer.

To find out more about how a coach can help students with ADHD achieve success, visit www.edgefoundation.org, a national nonprofit organization that provides coaching for students with ADHD. This organization also offers a free care package for the parents of teenagers or college students with ADHD that might prove helpful to the parents of your patients.[10]

Discussing the continued need for treatment

Attention-deficit/hyperactivity disorder is a complex disorder and patients will need a complex solution to ensure success. Treatment for ADHD is often described as being multimodal—comprised of many different components—and encompassing all aspects of daily life. Pediatricians of these patients may need to point out that ADHD affects not only the students' academic performance but also their relationships, emotions, and day-to-day activities such as eating, sleeping, and getting enough exercise. This is a lot to consider for such patients, but to foster success at the college level, these teenagers with ADHD will need to address their disorder and begin to take charge of their own care. The latter includes the use of medication, meaning that they need to become more knowledgeable about their medication and its effects. It is also important to discuss how taking medication might improve other aspects of daily life such as organization, time management, and relationships, in addition to academics.

Treatment issues to be discussed with patients with ADHD who are going off to college include: the decision to continue or even begin medication therapy at college; determining whether their current medication regimen is effective; a plan for developing communication strategies to convey their concerns back to you as their pediatrician once they are away at college; and how they will get their prescriptions filled on campus. Now is the time for pediatricians and their college-bound patients with ADHD to work together to develop a medication regimen that will lead to a practical daily schedule. Encouraging patients to take their medication consistently so that it will be effective for studying and reading assignments is often critical to a successful transition.

Over the last decade, several medications have been approved that make the treatment of ADHD easier and more effective. These newer medications are all longer-acting preparations in a variety of formulations and delivery systems (Table). Such once-a-day preparations provide the individual with ADHD a means of reducing symptoms throughout the day and into the early evening, while eliminating the need for a multiple-dose regimen that is difficult for those with ADHD to remember. In addition, longer-acting medications have fewer adverse effects, particularly

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the mood swings or "crash" seen in some patients as a short-acting medication is wearing off.[11,12]

Diversion of stimulant medications

Young adults on stimulant medications, particularly those living in dormitory or other communal settings, need to be reminded about several issues regarding these medications. First, they should be cautioned not to give or sell any of their ADHD medications to their friends or to others who ask for it. Not only does this reduce the amount of medication that they have for their own personal use, but it could also endanger the health of the other person.

In addition, it is important that patients understand that their medication is a controlled substance. Under federal law, ADHD medications are schedule II substances, and even giving these medications away can result in a drug distribution charge. Further, if patients use up their medication more quickly than prescribed or lose it, they will not be able to receive a new prescription until the end date of the current prescription. It may take some time to get a new prescription and have it filled, so students should be reminded to plan accordingly, especially around exam time. Finally, pediatricians should remind patients that, by law, these medications need to be kept in the original bottles and suggest that students carry their medications with them at all times to prevent theft.

Pursuing a healthy lifestyle

As students with ADHD pursue their college careers, they must do so in environments that are less structured and supportive than the ones they experienced in high school. This opportunity for growth and maturation is important, leading students with ADHD to work on their own to achieve balance and structure in their lives. Discussing ways to maintain good emotional and mental health, including how to deal with stress and how to get the emotional support through individual or group therapy or attending peer support groups on campus, is critical. The lifestyle of many college students often fails to include good

TABLE Longer-acting medications for attention-deficit/hyperactivity disorder

Generic	Brand	Description	Duration	Web site
Amphetamine/ Dextroamphetamine	Adderall XR	Extended release of mixed amphetamine salts; mimics bid dosing.	8-12 h	www.adderallxr.com
Dextroamphetamine	Dexedrine Spansule	Longer-acting amphetamine.	8-10 h	www.dexedrine.com
Lisdexamfetamine	Vyvanse	Prodrug activated in body; contains dexamphetamine.	12-14 h	www.vyvanse.com
Methylphenidate	Ritalin LA	Once-daily formulation; mimics bid dosing.	6-8 h	www.pharma.us.novartis.com/cs/www.pharma.us.novartis.com/product/pi/pdf/ritalin_la.pdf
	Metadate CD	Mimics bid dosing.	6-8 h	www.ucb.com/products/product-list/cns/metadate.asp
	Concerta	Mimics tid duration of action.	10-12 h	www.concerta360.com
Methylphenidate transdermal system	Daytrana	Patch can be worn for up to 9 h for 10 h efficacy.	10-12 h	www.daytrana.com

living habits such as eating a nutritionally sound, well-balanced diet with meals spaced evenly throughout the day; getting enough sleep; exercising regularly; and avoiding drugs and alcohol. Pediatricians can take this opportunity to reinforce the need for maintaining healthy habits.

A final word for pediatricians

The overall message of this article is one that urges pediatricians to hold deliberative discussions with college-bound patients with ADHD as early as possible in the college transition process. These discussions should encourage self-determination and the acquisition of independent living skills. By engaging college-bound students in this process, pediatricians are providing them the greatest opportunity to achieve success in college as well as in life. Given the trusting relationship that exists with these patients, pediatricians are likely in the best position to impart the critical information needed to ensure their successful transition to college.

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[a]Estimated from person-days at risk.

[b]Subjects in this portion of the study received 1 to 3 doses of PedvaxHIB.

[c]A lyophilized formulation was used in the study. A later study found the antibody response of Liquid PedvaxHIB to be comparable. The antibody responses induced by each formulation of PedvaxHIB were similar.

CI=confidence interval; DTP=diphtheria and tetanus toxoids and pertussis [vaccine]; OPV=oral polio vaccine; Hib=*Haemophilus influenzae* type b.

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PedvaxHIB is indicated for routine vaccination against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age. PedvaxHIB should not be used in infants <6 weeks of age.

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PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 6 WEEKS OF AGE.

PedvaxHIB is administered in a 2-dose primary regimen before 14 months of age. Infants 2 to 14 months of age should receive a 0.5 mL dose of vaccine, ideally beginning at 2 months of age, followed by a 0.5 mL dose 2 months later (or as soon as possible thereafter). When the primary 2-dose regimen is completed before 12 months of age, a booster dose (0.5 mL) should be administered at 12 to 15 months, but not earlier than 2 months after the second dose.

Select Safety Information

PedvaxHIB is contraindicated in patients with hypersensitivity to any component of the vaccine. Persons who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine.

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

The most frequently reported (>1%) adverse reactions, without regard to causality, were fever (≥101°F), irritability, sleepiness, injection-site pain/soreness, injection-site erythema (≤2.5 cm diameter), injection-site swelling/induration (≤2.5 cm diameter), unusual high-pitched crying, prolonged crying (>4 hours), diarrhea, vomiting, crying, pain, otitis media, rash, and upper respiratory infection.

As with any vaccine, vaccination may not result in a protective antibody response in all individuals given the vaccine. As with other vaccines, PedvaxHIB may not induce protective antibody levels immediately following vaccination.

Please see the adjacent Brief Summary of the Prescribing Information.

Reference: 1. Centers for Disease Control and Prevention. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind—United States, 2013. http://www.cdc.gov/vaccines/schedules/downloads/child/catchup-schedule-pr.pdf. Accessed February 19, 2013.

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Liquid PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]

INDICATIONS AND USAGE

Liquid PedvaxHIB is indicated for routine vaccination against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age.

Liquid PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease such as meningitis or sepsis. As with any vaccine, vaccination with Liquid PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine.

BECAUSE OF THE POTENTIAL FOR IMMUNE TOLERANCE, Liquid PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 6 WEEKS OF AGE. (See PRECAUTIONS in full Prescribing Information.)

Revaccination

Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION in full Prescribing Information).

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine or the diluent.

Persons who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine.

PRECAUTIONS

General

As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur.

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

As with other vaccines, Liquid PedvaxHIB may not induce protective antibody levels immediately following vaccination.

As reported with Haemophilus b Polysaccharide Vaccine and another Haemophilus b Conjugate Vaccine, cases of Hib disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines.

There is insufficient evidence that Liquid PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness.

The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. The Advisory Committee on Immunization Practices (ACIP) has recommended that vaccination should be delayed during the course of an acute febrile illness. All vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness. Persons with moderate or severe febrile illness should be vaccinated as soon as they have recovered from the acute phase of the illness.

If PedvaxHIB is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

Instructions to Healthcare Provider

The healthcare provider should determine the current health status and previous vaccination history of the vaccinee.

The healthcare provider should question the patient, parent, or guardian about reactions to a previous dose of PedvaxHIB or other Haemophilus b Conjugate Vaccines.

Information for Patients

The healthcare provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The healthcare provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see ADVERSE REACTIONS in full Prescribing Information.

Patients, parents, and guardians should be instructed to report any serious adverse reactions to their healthcare provider who in turn should report such events to the U. S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.

Laboratory Test Interactions

Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for at least 30 days following vaccination with lyophilized PedvaxHIB; in clinical studies with lyophilized PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Liquid PedvaxHIB has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with PedvaxHIB. Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older.

Pediatric Use

Safety and effectiveness in infants below the age of 2 months and in children 6 years of age and older have not been established. In addition, Liquid PedvaxHIB should not be used in infants younger than 6 weeks of age because this will lead to a reduced anti-PRP response and may lead to immune tolerance (impaired ability to respond to subsequent exposure to the PRP antigen). Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older because they are generally not at risk of Hib disease.

Geriatric Use

This vaccine is NOT recommended for use in adult populations.

ADVERSE REACTIONS

Liquid PedvaxHIB

In a multicenter clinical study (n=903) comparing the effects of Liquid PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] with those of lyophilized PedvaxHIB, 1,699 doses of Liquid PedvaxHIB were administered to 678 healthy infants 2 to 6 months of age from the general U.S. population. DTP and OPV were administered concomitantly to most subjects. Both formulations of PedvaxHIB were generally well tolerated and no serious vaccine-related adverse reactions were reported.

During a three-day period following primary vaccination with Liquid PedvaxHIB in these infants, the most frequently reported (>1%) adverse reactions, without regard to causality, excluding those shown in the table, in decreasing order of frequency, were: irritability, sleepiness, injection site pain/soreness, injection site erythema (≤2.5 cm diameter, see table), injection site swelling/induration (≤2.5 cm diameter, see table), unusual high-pitched crying, prolonged crying (>4 hr), diarrhea, vomiting, crying, pain, otitis media, rash, and upper respiratory infection.

Selected objective observations reported by parents over a 48-hour period in these infants following primary vaccination with Liquid PedvaxHIB are summarized in the following table.

Fever or Local Reactions in Subjects First Vaccinated at 2 to 6 Months of Age with Liquid PedvaxHIB[a]

Reaction	No. of Subjects Evaluated	Post-Dose 1 (hr)			No. of Subjects Evaluated	Post-Dose 2 (hr)		
		6	24	48		6	24	48
		Percentage				Percentage		
Fever[b] >38.3°C (≥101°F) Rectal	222	18.1	4.4	0.5	206	14.1	9.4	2.8
Erythema >2.5 cm diameter	674	2.2	1.0	0.5	562	1.6	1.1	0.4
Swelling >2.5 cm diameter	674	2.5	1.9	0.9	562	0.9	0.9	1.3

[a]DTP and OPV were administered concomitantly to most subjects.
[b]Fever was also measured by another method or reported as normal for an additional 345 infants after dose 1 and for an additional 249 infants after dose 2; however, these data are not included in this table.

Adverse reactions during a three-day period following administration of the booster dose were generally similar in type and frequency to those seen following primary vaccination.

Lyophilized PedvaxHIB

In The Protective Efficacy Study (see CLINICAL PHARMACOLOGY in full Prescribing Information), 4,459 healthy Navajo infants 6 to 12 weeks of age received lyophilized PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received lyophilized PedvaxHIB and those who received placebo, and none was reported to be related to lyophilized PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to lyophilized PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to lyophilized PedvaxHIB.

In early clinical studies involving the administration of 8,086 doses of lyophilized PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, lyophilized PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. In a subset of these infants, urticaria was reported in two children, and thrombocytopenia was seen in one child. A cause and effect relationship between these side effects and the vaccination has not been established.

Potential Adverse Reactions

The use of Haemophilus b Polysaccharide Vaccines and another Haemophilus b Conjugate Vaccine has been associated with the following additional adverse effects: early onset Hib disease and Guillain-Barré syndrome. A cause and effect relationship between these side effects and the vaccination was not established.

Post-Marketing Adverse Reactions

The following additional adverse reactions have been reported with the use of the lyophilized and liquid formulations of PedvaxHIB:

Hemic and Lymphatic System

Lymphadenopathy

Hypersensitivity

Rarely, angioedema

Nervous System

Febrile seizures

Skin

Sterile injection site abscess

For more detailed information, please read the full Prescribing Information.

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Early adenotonsillectomy eases sleep apnea

Compared with watchful waiting, surgical treatment of children with obstructive sleep apnea syndrome reduced symptoms and improved behavior, quality of life, and polysomnographic findings, according to a study of 464 children aged 5 to 9 years. Early adenotonsillectomy did not significantly improve attention or executive function compared with watchful waiting, however.

Children in the study, nearly half of whom were overweight or obese, were assigned to early adenotonsillectomy (surgery within 4 weeks of randomization) or to a watchful-waiting strategy. They underwent standardized polysomnographic testing, cognitive and behavioral testing, and other clinical and laboratory evaluations at baseline and again 7 months after randomization. For both examinations, caregivers completed survey instruments and teachers provided behavioral assessments.

Polysomnographic findings normalized in some patients in both groups during the study period but in a larger proportion of children in the early-adenotonsillectomy group than in the watchful-waiting group (79% vs 46%, respectively). Relative improvements with early adenotonsillectomy were significantly smaller among black children than among children of other races with regard to behavior, executive function, and sleep-related breathing disorder symptoms (Marcus CL, et al. *N Engl J Med*. 2013;368[25]:2366-2376).

COMMENTARY

The authors chose as the primary outcome of their study changes in measured scores of attention and executive function. For this outcome, they were unable to show a difference between the treatment and control groups. To be fair, this is a tough measure, especially since at baseline study participants had scores for this measure that were normal—no worse than the general population. This may reflect the exclusion from this study of children with severe sleep apnea, marked obesity, and attention-deficit/hyperactivity disorder on medication. It was in the secondary outcome measures that the results favored early surgical intervention in this group of children with mild-to-moderate, but not severe, sleep apnea. Most impressive was that a far larger proportion of children who had tonsillectomy showed normalized sleep studies at follow-up (79%) than children undergoing watchful waiting (46%)—a percentage point difference of more than 30. This means that for every 3 children treated with early tonsillectomy, measured sleep abnormalities will resolve in 1 child.

—Michael Burke, MD

ALMOST HALF OF TEENAGED DRIVERS TEXT WHEN BEHIND THE WHEEL

More than 44% of students at least 16 years old text while driving, data from the 2011 national Youth Risk Behavior Survey shows. About 8,500 teenagers responded to the survey question, "During the past 30 days, on how many days did you text or e-mail while driving a car or other vehicle?" The biennial survey, which is sponsored by the Centers for Disease Control and Prevention, was conducted in public and private high schools throughout the country; participation was anonymous and voluntary.

Of students who texted while driving, more than 1 in 4 did so on all 30 days. In addition, prevalence of any texting while driving increased with age, from 32.6% for 16-year-olds to 57.7% for students aged 18 years or older. The prevalence of any texting while driving also varied by race/ethnicity and was highest among white students (50.7%) and lowest among black students (30.1%). Boys were also more likely to engage in the activity than girls (46.4% vs 42.3%, respectively).

Furthermore, students who texted while driving were more likely than other teenaged drivers to engage

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in additional risky motor vehicle behaviors: to not always wear a seatbelt, to ride with a driver who has been drinking alcohol, or to drink alcohol and drive. Texting while driving and driving when drinking alcohol were most strongly associated, with students who texted while driving 5.4 times more likely to drive when they had been drinking than students who did not text while driving. In addition, the more a student texted while driving, the more likely he or she was to engage in other risky motor vehicle behaviors (O'Malley Olsen E, et al. *Pediatrics*. 2013;131[6]:e1708-e1715).

COMMENTARY

Despite increasing evidence that texting and cell phone use are linked with inattention among drivers, and despite increasing reports of individuals killed or injured while driving and texting, the practice of texting at the wheel is quite common and will be hard to change. Antitexting laws are difficult to enforce. We can educate parents and young drivers, but adolescence is marked by a sense of invulnerability and a focus on connecting with peers, which today means texting. I think that the solution will need to include some sort of "passive restraint" that deactivates phones when the car is moving. It may seem a little invasive, but it is what is most likely to work.

—Michael Burke, MD

ALLERGIES LESS PREVALENT IN FOREIGN-BORN AMERICANS

Compared with US-born American children, those born outside the United States are significantly less likely to develop allergic disease, a study in more than 91,600 children aged up to 17 years found. The odds of developing allergic disease significantly increased after residing in the United States for 1 decade or longer, however.

Investigators distributed questionnaires to participants who were enrolled in the 2007-2008 National Survey of Children's Health, and also conducted parent and child interviews. Analysis of collected data showed that 20.3% of children born outside the United States had any allergic disease compared with 34.5% of native-born children. In particular, children born outside the United States had lower odds of ever or current asthma, eczema, and hay fever.

In addition, children of parents born outside the United States were less likely to have any allergic diseases than those whose parents were native born, including ever and current asthma, eczema, hay fever, and food allergies. An additive effect also was observed, as children of 2 foreign-born parents had lower prevalence of allergic disorders than those with a single parent born outside the United States. In addition, children born outside the United States whose parents were also foreign born were less likely to have any allergic disease than those with US-born parents. Finally, compared with foreign-born children who lived in the United States only 0 to 2 years, those born elsewhere who lived in the United States for longer than 10 years were more likely to develop any allergic disorders (Silverberg JI, et al. *JAMA Pediatr*. 2013;167[6]:554-560).

COMMENTARY

Children who immigrate to the United States are less likely to have asthma, allergies, and atopic disease than native-born children. Their advantage is diminished if the immigrant children's parents were born in the United States and decreases the longer they are here. This may be a demonstration of the hygiene hypothesis with allergen exposure in the child's country of birth decreasing his or her allergic tendency. If that is the case, then either the protective effect of early antigen exposure wanes with time or children are exposed to other more allergenic proteins as they spend time here.

—Michael Burke, MD

Also of Note

Knowing limited English impacts a patient's quality of care in the pediatric emergency department (ED). A retrospective review of more than 119,700 patients discharged from a pediatric tertiary-care ED during a 2-year period found that patients (mean age, 7.6 years) whose primary language was not English were 1.3 times more likely than English speakers to have a return visit for admission within 72 hours of discharge. The increased risk remained significant after controlling for age, emergency severity index, and time of day (Gallagher RA, et al. *Pediatr Emerg Care*. 2013;29[5]:579-583).

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NEUROLOGIC COMPLICATIONS OF INFLUENZA IN CHILDREN

SANDRA S CHAVES, MD, MSC

Influenza-associated neurologic complications in children are rare, but can be severe. Familiarity with the clinical presentation and frequency of specific neurologic findings can help with early diagnosis and treatment.

In the United States, influenza epidemics occur every year, typically during the fall or winter months. Illness is often characterized by a combination of fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. Among children, diarrhea, nausea, and vomiting are not uncommon. In most cases, illness resolves within 3 to 7 days, although cough and malaise can persist for more than 2 weeks. However, influenza can be severe and lead to hospitalization and death.

Children at increased risk for developing severe influenza and related complications include those aged younger than 5 years; children with certain medical conditions, especially those with chronic pulmonary (including asthma), cardiovascular, renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus); children who are immunosuppressed (eg, from medications or human immunodeficiency virus); and children receiving long-term aspirin therapy and who therefore might be at risk for experiencing Reye syndrome after influenza virus infection.[1]

Common influenza-associated complications include primary influenza viral pneumonia, otitis media, and exacerbation of underlying medical conditions (eg, pulmonary, metabolic, or cardiac diseases). In addition, influenza may lead to secondary bacterial pneumonia or contribute to co-infections with other viral or bacterial pathogens.[2] Neurologic complications associated with influenza virus infection also occur; most reports have been in children, possibly reflecting high influenza attack rates in this age group. Although neurologic complications of influenza are less common than other sequelae, familiarity with the clinical spectrum and features is important for clinicians to optimize clinical management.

Neurologic complications associated with influenza in children

Influenza has been associated with a variety of neurologic complications of varying severity (Table 1). The most common neurologic manifestations are seizures with and without fever and altered sensorium.[3-6] More severe manifestations include Guillain-Barré syndrome (GBS),[7] stroke, focal

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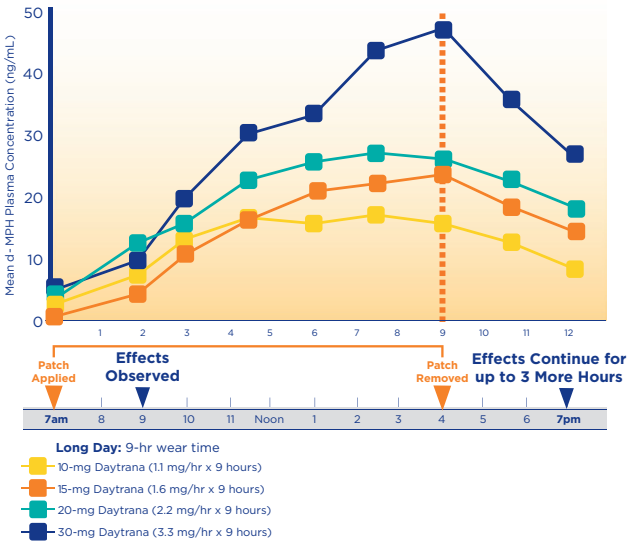
Daytrana® (methylphenidate transdermal system) 10 mg 15 mg 20 mg 30 mg

Daytrana®: The Only Transdermal ADHD Medication

- Smooth and consistent MPH levels
- Long-acting symptom control
- Removable to control duration

The Daytrana patch, as with other stimulants, is subject to abuse and dependence requiring appropriate patient selection and supervision.

Smooth, Consistent Plasma Levels



Study 201: Drug concentration from multiple-dose administration of Daytrana® in a randomized, double-blind, placebo-controlled laboratory pediatric classroom study. Plasma samples were obtained for pharmacokinetic analysis at predose and 2, 3, 4.5, 6, 7.5, 9, 10.5, and 12 hours after dose administration. (10 mg) n=7; (15 mg) n=32; (20 mg) n=27; (30 mg) n=8.[1,2]

INDICATION

The Daytrana® patch is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children (ages 6-12) and adolescents (ages 13-17). The efficacy of the Daytrana® patch was established in controlled clinical studies: two 7-week trials in children and one 7-week trial in adolescents. Diagnosis of ADHD is based on complete patient history and evaluation, not just DSM-IV-TR® characteristics. The Daytrana® patch is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, and social).

IMPORTANT SAFETY INFORMATION

WARNING: DRUG DEPENDENCE

Daytrana® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

CONTRAINDICATIONS: The Daytrana® patch should not be used by patients who have an allergy to methylphenidate, acrylic adhesive, or silicone adhesive; marked anxiety, tension, and agitation; glaucoma; motor tics or with a diagnosis or a family history of Tourette's syndrome; are being treated (or within 14 days after treatment) with monoamine oxidase inhibitors (MAOIs).

SERIOUS CARDIOVASCULAR EFFECTS: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. A careful patient history, including family history, and physical exam should be performed to assess the presence of cardiac disease. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. Patients who develop symptoms (i.e., exertional chest pain, unexplained syncope) suggestive of cardiac disease while using or wearing the Daytrana® patch should be promptly evaluated. Use with caution in patients whose underlying medical condition might be affected by increases in blood pressure or heart rate. Use cautiously with pressor agents. Hematologic monitoring is advised during prolonged treatment.

PSYCHIATRIC, SEIZURES, AND GROWTH SUPPRESSION: Use with caution in patients with a history of psychosis, bipolar disorder, depression, seizures, or EEG abnormalities. New psychosis, mania, aggression, seizures, visual disturbances, and growth suppression have been associated with the use of stimulants. Growth should be monitored in children during treatment with stimulants, and patients who are not growing (gaining height or weight) as expected may need to suspend treatment with the Daytrana® patch.

CONTACT SENSITIZATION: Use of the Daytrana® patch may lead to contact sensitization. Erythema has been commonly reported and is not by itself an indication of sensitization. If contact sensitization is suspected (erythema with edema, papules and/or vesicles spread beyond the patch site and/or lack of improvement within 48 hours), treatment should be discontinued. Patients should avoid applying external heat to the Daytrana® patch; application of heat can increase the extent and rate of absorption.

MOST COMMON ADVERSE EVENTS: The most common adverse reactions associated with the Daytrana® patch (at least 5% and twice the rate of placebo-treated patients) in clinical trials were: children – decreased appetite, insomnia, nausea, vomiting, decreased weight, tics, affect lability, and anorexia; adolescents – decreased appetite, nausea, insomnia, decreased weight, dizziness, abdominal pain, and anorexia. In addition, the majority of subjects in these studies had minimal to definite skin erythema at the patch application site. Leaving the patch on for longer than the recommended 9 hours has resulted in an increased incidence of adverse events.

Please read Brief Summary Full Prescribing Information on next page, including Medication Guide and Boxed Warning regarding Drug Dependence.

1. Wigal SB, Pierce DM, Dixon CM, McGough JJ. Pharmacokinetics of methylphenidate transdermal system in children with ADHD. Poster presented at: 18th Annual US Psychiatric and Mental Health Congress; November 8, 2005; Las Vegas, Nev.
2. McGough JJ, Wigal SB, Abikoff H, et al. A randomized, double-blind, placebo-controlled, laboratory classroom assessment of methylphenidate transdermal system in children with ADHD. J Atten Disord. 2006;9:47-485.

Please read Important Safety Information above and Brief Summary Full Prescribing Information on next page, including **Medication Guide** and **Boxed Warning regarding Drug Dependence.**

NOVEN THERAPEUTICS, LLC

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DAYTRANA® CII (methylphenidate transdermal system) Noven Therapeutics, LLC

Brief Summary. Consult Package Insert for complete prescribing information.

WARNING: DRUG DEPENDENCE

Daytrana should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

1 INDICATIONS AND USAGE

Daytrana (methylphenidate transdermal system) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Daytrana in patients diagnosed with ADHD was established in two 7-week controlled clinical trials in children (ages 6-12) and one 7-week, controlled clinical trial in adolescents (ages 13-17).

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Methylphenidate - Daytrana is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product (polyester/ethylene vinyl acetate laminate film backing, acrylic adhesive, silicone adhesive, and fluoropolymer-coated polyester). **4.2 Agitation** - Daytrana is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms. **4.3 Glaucoma** - Daytrana is contraindicated in patients with glaucoma. **4.4 Tics** - Daytrana is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome [see Adverse Reactions (6.1)]. **4.5 Monoamine Oxidase Inhibitors** - Daytrana is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises may result).

5 WARNINGS and PRECAUTIONS

5.1 Serious Cardiovascular Events ***Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems*** *Children and Adolescents:* Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug. *Adults:* Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs. ***Hypertension and Other Cardiovascular Conditions*** Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia [see Adverse Reactions (6.1)]. ***Assessing Cardiovascular Status in Patients Being Treated With Stimulant Medications*** Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation. **Peripheral Vasculopathy:** 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. **5.2 Psychiatric Adverse Events** *Pre-Existing Psychosis:* Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. Bipolar Illness: Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. *Emergence of New Psychotic or Manic Symptoms:* Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3,482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to none in placebo-treated patients. *Aggression:* Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility. **5.3 Seizures** - There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued. **5.4 Long-Term Suppression of Growth** - Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children 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 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. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. **5.5 Visual Disturbance** - Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. **5.6 Contact Sensitization** - In an open-label study of 305 subjects conducted to characterize dermal reactions in children with ADHD treated with Daytrana using a 9-hour wear time, one subject (0.3%) was confirmed by patch testing to be sensitized to methylphenidate (allergic contact dermatitis). This subject experienced erythema and edema at Daytrana application sites with concurrent urticarial lesions on the abdomen and legs resulting in treatment discontinuation. This subject was not transitioned to methylphenidate. Use of Daytrana may lead to contact sensitization. Daytrana should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of Daytrana and is not by itself an indication of sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site. Confirmation of a diagnosis of contact sensitization (allergic contact dermatitis) may require further diagnostic testing. Patients sensitized from use of Daytrana, as evidenced by development of an allergic contact dermatitis, may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes, e.g., orally. Manifestations of systemic sensitization may include a flare-up of previous dermatitis or of prior positive patch-test sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, diarrhea, or vomiting. No cases of systemic sensitization have been observed in clinical trials of Daytrana. Patients who develop contact sensitization to Daytrana and require oral treatment with methylphenidate should be initiated on oral medication under close medical supervision. It is possible that some patients sensitized to methylphenidate by exposure to Daytrana may not be able to take methylphenidate in any form. **5.7 Patients Using External Heat** - Patients should be advised to avoid exposing the Daytrana application site to direct external heat sources, such as hair dryers, heating pads, electric blankets, heated water beds, etc., while wearing the patch. When heat is applied to Daytrana after patch application, both the rate and extent of absorption are significantly increased. The temperature-dependent increase in methylphenidate absorption can be greater than 2-fold. This increased absorption can be clinically significant and can result in overdose of methylphenidate [see Overdosage (10)]. **5.8 Hematologic Monitoring** - Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

6 ADVERSE REACTIONS

Detailed information on serious and adverse reactions of particular importance is provided in the Boxed Warning and Warnings and Precautions (5) sections: • Drug dependence [see Boxed Warning] • Hypersensitivity to Methylphenidate [see Contraindications (4.1)] • Marked anxiety, tension, or agitation [see Contraindications (4.2)] • Glaucoma [see Contraindications (4.3)] • Tics or a family history of Tourette's syndrome [see Contraindications (4.4)] • Monoamine Oxidase Inhibitors [see Contraindications (4.5) and Drug Interactions (7.1)] • Serious Cardiovascular Events [see Warnings and Precautions (5.1)] • Increase in Blood Pressure [see Warnings and Precautions (5.2)] • Psychiatric Adverse Events [see Warnings and Precautions (5.2)] • Seizures [see Warnings and Precautions (5.3)] • Long-Term Suppression of Growth [see Warnings and Precautions (5.4)] • Visual Disturbance [see Warnings and Precautions (5.5)] • Contact Sensitization [see Warnings and Precautions (5.6)] • External Heat [see Warnings and Precautions (5.7)] • Hematologic Monitoring [see Warnings and Precautions (5.8)] The most commonly reported (frequency ≥ 5% and twice the rate of placebo) adverse reactions in a controlled trial in children aged 6-12 included appetite decreased, insomnia, nausea, vomiting, weight decreased, tic, affect lability, and anorexia. The most commonly reported (frequency ≥ 5% and twice the rate of placebo) adverse reactions in a controlled trial in adolescents aged 13-17 were appetite decreased, nausea, insomnia, weight decreased, dizziness, abdominal pain and anorexia [see Adverse Reactions (6.1)]. The most common (≥ 2% of subjects) adverse reaction associated with discontinuations in double-blind clinical trials in children or adolescents was application site reactions15 [see Adverse Reactions (6.3)]. The overall Daytrana development program included exposure to Daytrana in a total of 2,152 participants in clinical trials, including 1,529 children aged 6-12, 223 adolescents aged 13-17, and 400 adults. The 1,752 child and adolescent subjects aged 6-17 years were evaluated in 10 controlled clinical studies, 7 open-label clinical studies, and 5 clinical pharmacology studies. In a combined studies pool of children using Daytrana with a wear time of 9 hours, 212 subjects were exposed for ≥ 6 months and 115 were exposed for ≥ 1 year; 85 adolescents have been exposed for ≥ 6 months. Most patients studied were exposed to Daytrana patch sizes of 12.5 cm2, 18.75 cm2, 25 cm2 or 37.5 cm2, with a wear time of 9 hours. In the data presented below, the adverse reactions reported during exposure were obtained primarily by general inquiry at each visit, and were recorded by the clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of events into a smaller number of standardized event categories. Throughout this section adverse reactions reported are events that were considered to be reasonably associated with the use of Daytrana based on comprehensive assessment of the available adverse event information. A causal association for Daytrana often cannot be reliably established in individual cases. Further, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.1 Clinical Trials Experience *Adverse Reactions Associated With Discontinuation of Treatment* In a 7-week double-blind, parallel-group, placebo-controlled study in children with ADHD conducted in the outpatient setting, 7.1% (7/98) of patients treated with Daytrana discontinued due to adverse events compared with 1.2% (1/85) receiving placebo. The most commonly reported (≥ 1% and twice the rate of placebo) adverse reactions leading to discontinuation in the Daytrana group were application site reaction (2%), tics (1%), headache (1%), and irritability (1%). In a 7-week double-blind, parallel-group, placebo-controlled study in adolescents with ADHD conducted in the outpatient setting, 5.5% (8/145) of patients treated with Daytrana discontinued due to adverse reactions compared with 2.8% (2/72) receiving placebo. The most commonly reported adverse reactions leading to discontinuation in the Daytrana group were application site reaction (2%) and decreased appetite/anorexia (1.4%). *Commonly Observed Adverse Reactions in Double-Blind, Placebo-Controlled Trials Skin Irritation and Application Site Reactions:* Daytrana is a dermal irritant. In addition to the most commonly reported adverse reactions presented in Table 2, the majority of subjects in those studies had minimal to definite skin erythema at the patch application site. This erythema generally caused no or minimal discomfort and did not usually interfere with therapy or result in discontinuation from treatment. Erythema is not by itself a manifestation of contact sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site [see Warnings and Precautions (5.6)]. *Most Commonly Reported Adverse Reactions:* Table 2 lists treatment-emergent adverse reactions reported in ≥ 1% Daytrana-treated children or adolescents with ADHD in two 7 week double-blind, parallel-group, placebo-controlled studies conducted in the outpatient setting. Overall, in these studies, 75.5% of children and 78.6% of adolescents experienced at least 1 adverse event. *Adverse Reactions With the Long-Term Use of Daytrana:* In a long-term open-label study of up to 12 months duration in 326 children wearing Daytrana 9 hours daily, the most common (≥ 10%) adverse reactions were decreased appetite, headache, and weight decreased. A total of 30 subjects (9.2%) were withdrawn from the study due to adverse events and 22 additional subjects (6.7%) discontinued treatment as the result of an application site reaction. Other than application site reactions, affect lability (5 subjects, 1.5%) was the only additional adverse reaction leading to discontinuation reported with a frequency of greater than 1%. In a long-term open-label study of up to 6 months duration in 162 adolescents wearing Daytrana 9 hours daily, the most common (≥ 10%) adverse reactions were decreased appetite and headache. A total of 9 subjects (5.5%) were withdrawn from the study due to adverse events and 3 additional subjects (1.9%) discontinued treatment as the result of an application site reaction. Other adverse reactions leading to discontinuation that occurred with a frequency of greater than 1% included affect lability and irritability (2 subjects each, 1.2%).

Table 2 - Number (%) of Subjects with Commonly Reported Adverse Reactions (≥ 1% in the Daytrana Group) in 7-Week Placebo-controlled Studies in Either Children or Adolescents - Safety Population

	Adolescents		Children	
System Organ Class Preferred term	Placebo N = 72	Daytrana N = 145	Placebo N = 85	Daytrana N = 98
Cardiac Disorders				
Tachycardia	0 (0)	1 (0.7)	0 (0)	1 (1.0)
Gastrointestinal disorders				
Abdominal pain	0 (0)	7 (4.8)	5 (5.9)	7 (7.1)
Nausea	2 (2.8)	14 (9.7)	2 (2.4)	12 (12.2)
Vomiting	1 (1.4)	5 (3.4)	4 (4.7)	10 (10.2)
Investigations				
Weight decreased	1 (1.4)	8 (5.5)	0 (0)	9 (9.2)
Metabolism and nutrition disorders				
Anorexia	1 (1.4)	7 (4.8)	1 (1.2)	5 (5.1)
Decreased appetite	1 (1.4)	37 (25.5)	4 (4.7)	25 (25.5)
Nervous system disorders				
Dizziness	1 (1.4)	8 (5.5)	1 (1.2)	0 (0)
Headache	9 (12.5)	18 (12.4)	10 (11.8)	15 (15.3)
Psychiatric disorders				
Affect lability	1 (1.4)	0 (0)	0 (0)	6 (6.1)*
Insomnia	2 (2.8)	9 (6.2)	4 (4.7)	13 (13.3)
Irritability	5 (6.9)	16 (11)	4 (4.7)	7 (7.1)
Tic	0 (0)	0 (0)	0 (0)	7 (7.1)

* Six subjects had affect lability, all judged as mild and described as increased emotionally sensitive, emotionality, emotional instability, emotional lability, and intermittent emotional

6.2 Postmarketing Experience In addition, the following adverse reactions have been identified during the post-approval use of Daytrana. 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 Daytrana exposure. *Cardiac Disorders:* palpitation. *Eye Disorders:* visual disturbances, blurred vision, mydriasis, accommodation disorder. *General Disorders and Administration Site Disorders:* application site reactions such as bleeding, bruising, burn, burning, dermatitis, discharge, discoloration, discomfort, dryness, eczema, edema, erosion, erythema, excoriation, exfoliation, fissure, hyperpigmentation, hypopigmentation, induration, infection, inflammation, irritation, pain, papules, paresthesia, pruritus, rash, scab, swelling, ulcer, urticaria, vesicles, and warmth. *Immune System Disorders:* hypersensitivity reactions including generalized erythematous and urticarial rashes, allergic contact dermatitis, angioedema, and anaphylaxis. *Investigations:* blood pressure increased. *Nervous System Disorders:* convulsion, dyskinesia. *Psychiatric Disorders:* transient depressed mood, hallucination, nervousness. *Skin and Subcutaneous Tissue Disorders:* alopecia **6.3 Adverse Reactions With Oral Methylphenidate Products** Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur. Other reactions include: *Cardiac:* angina, arrhythmia, pulse increased or decreased. *Immune:* hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura. *Metabolism/Nutrition:* anorexia, weight loss during prolonged therapy. *Nervous System:* drowsiness, rare reports of Tourette's syndrome, toxic psychosis. *Vascular:* blood pressure increased or decreased, cerebral arteritis and/or occlusion. Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate: *Blood/lymphatic:* leukopenia and/or anemia. *Hepatobiliary:* abnormal liver function, ranging from transaminase elevation to hepatic coma. *Psychiatric:* transient depressed mood. *Skin/Subcutaneous:* scalp hair loss. *Neuroleptic Malignant Syndrome:* Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

7 DRUG INTERACTIONS

7.1 MAO Inhibitors - Daytrana should not be used in patients being treated (currently or within the preceding two weeks) with monoamine oxidase inhibitors [see Contraindications (4.5)]. **7.2 Vasopressor Agents** - Because of a possible effect on blood pressure, Daytrana should be used cautiously with pressor agents. **7.3 Hypotension Agents** - Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. **7.4 Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors** - Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some tricyclic drugs (e.g., imipramine, clomipramine, desipramine) and selective serotonin reuptake inhibitors. Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing methylphenidate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: *Pregnancy Category C* - Animal reproduction studies with transdermal methylphenidate have not been performed. In a study in which oral methylphenidate was given to pregnant rabbits during the period of organogenesis at doses up to 200 mg/kg/day no teratogenic effects were seen, although an increase in the incidence of a variation, dilation of the lateral ventricles, was seen at 200 mg/kg/day; this dose also produced maternal toxicity. A previously conducted study in rabbits showed teratogenic effects of methylphenidate at an oral dose of 200 mg/kg/day. In a study in which oral methylphenidate was given to pregnant rats during the period of organogenesis at doses up to 100 mg/kg/day, no teratogenic effects were seen although a slight delay in fetal skeletal ossification was seen at doses of 60 mg/kg/day and above; these doses caused some maternal toxicity. In a study in which oral methylphenidate was given to rats throughout pregnancy and lactation at doses up to 60 mg/kg/day, offspring weights and survival were decreased at 40 mg/kg/day and above; these doses caused some maternal toxicity. Adequate and well-controlled studies in pregnant women have not been conducted. Daytrana should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **8.2 Labor and Delivery** - The effect of Daytrana on labor and delivery in humans is unknown. **8.3 Nursing Mothers** - It is not known whether methylphenidate is excreted in human milk. Daytrana should be administered to a nursing woman only if the potential benefit justifies the potential risk to the child. **8.4 Pediatric Use** - Daytrana should not be used in children under six years of age, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established. Studies with transdermal methylphenidate have not been performed in juvenile animals. In a study conducted in young rats, methylphenidate was 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 or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose. The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day. The clinical significance of the long-term behavioral effects observed in rats is unknown. **8.5 Geriatric Use:** Daytrana has not been studied in patients greater than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance - Daytrana is classified as a Schedule II controlled substance by federal regulation. **9.2 Abuse** - See warning containing drug abuse information [see Boxed Warning]. **9.3 Dependence** - See warning containing drug dependence information [see Boxed Warning].

Manufactured for: Noven Therapeutics, LLC. Miami, FL 33186 By: Noven Pharmaceuticals, Inc., Miami, FL 33186. For more information call 1-877-567-7857 or visit WWW.DAYTRANA.COM. Dot Matrix™ is a trademark of Noven Pharmaceuticals, Inc. Daytrana® is a registered trademark of Noven Therapeutics, LLC. This product is covered by US patents including for use with 6,905,016. Last Modified: 06/2013 102086-12 Revised: 06/2013 Noven Therapeutics, LLC. DAY-1002-13 06/13

TABLE 1 Neurologic complications associated with influenza

- Seizure (including febrile seizure and seizure without fever)
- Encephalopathy/Encephalitis (including acute necrotizing encephalitis)
- Stroke
- Myelitis
- Meningitis
- Focal neurologic deficit (including extremity paralysis)
- Guillain-Barré syndrome

neurologic deficits, acute disseminated encephalomyelitis, encephalopathy, and transverse myelitis.[5,8,9] In the 1980s, the use of salicylates in children with viral infections (including influenza) was found to be associated with Reye syndrome, a neurologic condition consisting of severe encephalopathy, hepatic microvesicular fatty change, and hyperammonemia. This syndrome is currently rare in the United States, possibly because of public education on the dangers of salicylate use in children with an acute viral infection.[10]

Virus strain-specific associations with neurologic complications have been described in the literature. For example, some studies have associated encephalitis lethargica with the influenza A (H1N1) strain circulating during the pandemic of 1918-1919.[11] In the 1990s, investigators in Japan reported many cases of encephalopathy/encephalitis with high mortality in children that were thought to be associated with the influenza A (H3N2) virus strain circulating at that time.[12,13] It remains unclear, however, whether aspects of the clinical presentation and severity of neurologic manifestations truly vary with specific circulating strains.

A number of recent reports have focused on neurologic manifestations associated with the pandemic influenza A (H1N1)pdm09 virus.[14-17] Attempts to compare the neurologic manifestations described during the 2009 pandemic with those associated with seasonal influenza were mostly inconclusive due to the small number of observations and changes in case ascertainment (less sensitive influenza tests used before the 2009 influenza pandemic combined with heightened awareness of influenza-related complications during the pandemic).

Frequency of neurologic complications associated with influenza in children

Based on a retrospective cohort study of US patients hospitalized with laboratory-confirmed influenza, from the 2000-2001 through 2003-2004 seasons, the incidence of neurologic complications associated with influenza was approximately 4 cases per 100,000 children-years; patients aged between 2 and 4 years and with preexisting neurologic or neuromuscular disease were at greatest risk.[8]

During the 2009 influenza pandemic, another population-based study looked at potential neurologic complications associated with laboratory-confirmed influenza in patients who were admitted to the intensive care unit (ICU) or died.[4] Of all ICU and fatal cases, 3.7% were identified as having influenza-associated neurologic complications; the median age was 9 years. The researchers estimated that 1.2 severe neurologic complications occurred for every 100,000 persons with symptomatic influenza A (H1N1)pdm09 virus infection.

Data on the clinical spectrum and epidemiology of the various neurologic manifestations associated with influenza virus infection are still limited. Because of varying case definitions and case ascertainment, the frequency of neurologic manifestations associated with influenza is likely to be underestimated.

SEIZURES

Seizures are the most frequently reported neurologic complication associated with influenza. Febrile seizures have been reported in up to 20% of children aged 6 months through 5 years hospitalized with influenza.[3,18] This is higher than the background rate of febrile seizure of 2% to 5% estimated for this age group.[19]

The majority of children with influenza-associated febrile seizures will have a single uncomplicated partial or generalized seizure.[3,16] However, as many as one-third of these children may have prolonged seizures of more than 15 minutes or multiple seizures within 24 hours, and some can require ICU support and/or mechanical ventilation.[3-5] Beyond the typical age at which febrile seizures are common, older children who have seizures associated with influenza are more likely to have a previous diagnosis of epilepsy or encephalopathy/encephalitis.[6]

Although most patients with influenza-associated seizures do not have abnormalities on the electroencephalogram (EEG) or on neuroimaging,[6,16] those with EEG abnormalities may have diffuse slowing,

spike and wave discharges, or a burst suppression pattern.[6] In rare instances, magnetic resonance imaging (MRI) of the brain has shown increased T2 signal changes in the hippocampus and splenium or mild gyral swelling consistent with meningoencephalitis. However, cerebrospinal fluid (CSF) cell counts, glucose level, and protein level are usually within normal limits. In most case reports, patients with influenza-associated seizures survived with no residual neurologic sequelae.[3-6] When seizures are associated with severe neurologic complications, such as encephalopathy or encephalitis, the prognosis can be somber.

ENCEPHALOPATHY (WITH OR WITHOUT SEIZURES)

Encephalopathy/encephalitis appears to be the second most common neurologic complication associated with influenza. It is usually defined as altered mental status lasting for more than 24 hours, but its clinical spectrum can vary from mild confusion to behavioral changes, delirium/hallucination, meaningless speech, mutism/aphasia, lethargy, somnolence, and coma. Neuropsychiatric behaviors have been associated with influenza as part of the clinical spectrum of encephalopathy/encephalitis.[5,8,20] Children or adolescents may present within the first 3 days of influenza with delirium characterized by visual hallucinations, inappropriate laughing or smiling, meaningless words, incoherent speech, and restlessness, and the MRI scan and EEG are often normal.[17,20,21]

There have been attempts to separate encephalopathy from encephalitis based on the presence of central nervous system (CNS) inflammation. For instance, only a few patients with influenza-associated encephalopathy have elevated protein or mild pleocytosis in the CSF; in most cases CSF is normal.[13,22] Neuroimaging abnormalities have been described and include focal or generalized cerebral edema.[22] Nonetheless, it is difficult to assess accurately the level of CNS inflammation or the patient's prognosis based on neuroimaging results.

Most case series of encephalopathy come from Japan, Taiwan, and Korea, which suggests that the disease could be more common in these areas, although there is no clear explanation for a geographic predisposition. The cases of encephalopathy in Japan have been described as severe, with a high fatality rate.[12,13] Morishima and colleagues described 148 cases of encephalitis or encephalopathy identified in Japan during the 1999 influenza season, and more than 80% of those cases occurred in children aged younger than 5 years.[12] Approximately 10% of those cases had imaging studies consistent with acute necrotizing encephalopathy. Of the total 148 patients, 32% died and 28% had long-term sequelae.

Acute necrotizing encephalopathy is a severe type of encephalopathy associated with influenza and other viral infections such as mycoplasma, herpes simplex virus, and human herpesvirus 6. The condition causes bilateral necrosis of the thalami and other regions, including the cerebral white matter, cerebellum, and brain stem.[23,24] The patient's mental status can deteriorate rapidly to coma; permanent neurologic sequelae or death is not uncommon.

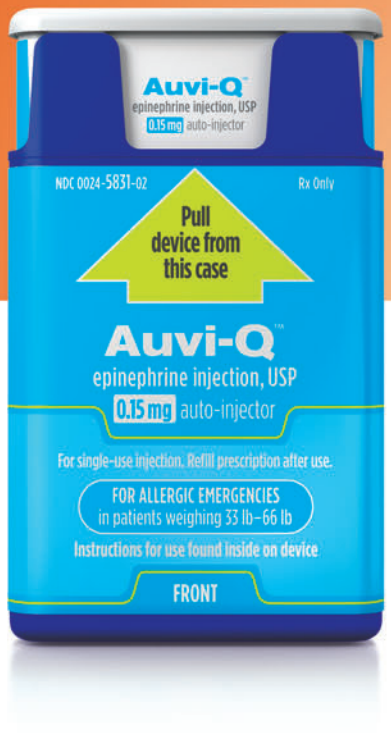
A population-based study from California found 29 patients with encephalopathy/encephalitis out of 77 with neurologic complications associated with influenza A (H1N1)pdm09; 55% were pediatric patients.[4] In these patients, CSF was generally unremarkable and only 3 patients had abnormal neuroimaging (2 had significant edema and 1 had bilateral frontal, temporal, and thalamic signal abnormalities consistent with acute necrotizing encephalitis). In contrast to the reports from Japan, most patients had good clinical outcomes and returned to their baseline status before hospital discharge.

A study from Australia described neurologic complications associated with influenza A (H1N1)pdm09 in 49 children; 55% had preexisting comorbid conditions.[25] Among all cases with influenza infection (N=506), 7 (1.4%) had encephalitis/encephalopathy and 5 of them needed ICU treatment; 1 died. In both studies, encephalopathy/encephalitis generally occurred shortly after the onset of respiratory symptoms and was rapidly progressive.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome may be described as a collection of clinical syndromes manifesting as an acute inflammatory polyradiculoneuropathy and resulting in weakness and diminished reflexes. Children usually complain of difficulty in climbing stairs. The child may complain of paresthesia of the feet followed by leg, buttock, or back pain, which likely result from nerve root and peripheral nerve inflammation.

What does Auvi-Q offer my patients at risk for anaphylaxis?



I talk.

Auvi-Q is available for adults and children weighing greater than 33 lb. Features include:

- **Audio and Visual Cues** guide users step by step through the injection process
- **Press-and-Hold** injection mechanism with 5-second hold time
- **Retractable Needle** designed to help prevent accidental needle sticks
- **Unique Compact Size and Shape**

Indication
Auvi-Q™ (epinephrine injection, USP) is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to allergens, idiopathic and exercise-induced anaphylaxis. Auvi-Q is intended for individuals with a history of anaphylaxis or who are at risk for anaphylactic reactions.

Important Safety Information
Auvi-Q should **ONLY** be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK OR INTRAVENOUSLY.

Epinephrine should be administered with caution to patients with certain heart diseases, and in patients who are on medications that may sensitize the heart to arrhythmias, because it may precipitate or aggravate angina pectoris and produce ventricular arrhythmias. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or taking cardiac glycosides or diuretics. Patients with certain medical conditions or who take certain medications for allergies, depression, thyroid disorders, diabetes, and hypertension, may be at greater risk for adverse reactions. Adverse reactions to epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

Auvi-Q is intended for immediate self-administration as emergency supportive therapy only and is not a substitute for immediate medical or hospital care.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see brief summary of Prescribing Information on the next page.

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0.15 mg/0.3 mg auto-injectors
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Auvi-Q™ **Rx Only**
(epinephrine injection, USP) 0.3 mg, 0.15 mg Auto-Injector

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

Auvi-Q™ is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

Auvi-Q™ is intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.

Anaphylactic reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.

Auvi-Q™ is intended for immediate self-administration as emergency supportive therapy only and is not a substitute for immediate medical care.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 EMERGENCY TREATMENT

Auvi-Q™ is not intended as a substitute for immediate medical care. **In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care.** More than two sequential doses of epinephrine should only be administered under direct medical supervision [*see INDICATIONS AND USAGE (1), DOSAGE AND ADMINISTRATION (2) and PATIENT COUNSELING INFORMATION (17.1 in the full prescribing information)*].

5.2 INCORRECT LOCATIONS OF INJECTION

Auvi-Q™ should **ONLY** be injected into the anterolateral aspect of the thigh [*see DOSAGE AND ADMINISTRATION (2) and PATIENT COUNSELING INFORMATION (17.1 in the full prescribing information)*].

- **Do not inject intravenously.** Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.
- **Do not inject into buttock.** Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis.
- **Do not inject into digits, hands or feet.** Since epinephrine is a strong vasoconstrictor, accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area. Advise the patient to go immediately to the nearest emergency room and to inform the healthcare provider in the emergency room of the location of the accidental injection. Treatment of such inadvertent administration should consist of vasodilation, in addition to further appropriate treatment of anaphylaxis [*see ADVERSE REACTIONS (6)*].

5.3 ALLERGIC REACTIONS ASSOCIATED WITH SULFITE

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium bisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons.

The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive.

The alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

5.4 DISEASE INTERACTIONS

Some patients may be at greater risk for developing adverse reactions after epinephrine administration. Despite these concerns, it should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation. Therefore, patients with these conditions, and/or any other person who might be in a position to administer Auvi-Q™ to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

- Patients with Heart Disease
  Epinephrine should be administered with caution to patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias [*see DRUG INTERACTIONS (7) and ADVERSE REACTIONS (6)*].
- Other Patients and Diseases
  Epinephrine should be administered with caution to patients with hyperthyroidism, diabetes, elderly individuals, and pregnant women. Patients with Parkinson's disease may notice a temporary worsening of symptoms.

6 ADVERSE REACTIONS

Adverse reactions to epinephrine include anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism [*see WARNINGS AND PRECAUTIONS (5.4)*].

Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs [*see WARNINGS AND PRECAUTIONS (5.4) and DRUG INTERACTIONS (7)*].

Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [*see WARNINGS AND PRECAUTIONS (5.4)*].

Angina may occur in patients with coronary artery disease [*see WARNINGS AND PRECAUTIONS (5.4)*].

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area [*see WARNINGS AND PRECAUTIONS (5.2)*].

Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pallor, coldness and hypoesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

7 DRUG INTERACTIONS

Patients who receive epinephrine while concomitantly taking cardiac glycosides, diuretics, or anti-arrhythmics should be observed carefully for the development of cardiac arrhythmias [*see WARNINGS AND PRECAUTIONS (5.4)*].

The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripelennamine, and diphenhydramine.

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs, such as propranolol.

The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs, such as phentolamine.

Ergot alkaloids may also reverse the pressor effects of epinephrine.

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well controlled studies of the acute effect of epinephrine in pregnant women.

Epinephrine was teratogenic in rabbits, mice and hamsters. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (fetal anoxia, spontaneous abortion, or both).

Epinephrine has been shown to have teratogenic effects when administered subcutaneously in rabbits at approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal dose of 1.2 mg/kg/day for two to three days), in mice at approximately 7 times the maximum daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 1 mg/kg/day for 10 days), and in hamsters at approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5 mg/kg/day for 4 days).

These effects were not seen in mice at approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 10 days).

8.3 NURSING MOTHERS

It is not known whether epinephrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Auvi-Q™ is administered to a nursing woman.

8.4 PEDIATRIC USE

Auvi-Q™ may be given safely to pediatric patients at a dosage appropriate to body weight [*see DOSAGE AND ADMINISTRATION (2)*]. However, studies in pediatric patients weighing less than 15 kg (33 pounds) have not been conducted.

8.5 GERIATRIC USE

Clinical studies of Auvi-Q™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Epinephrine should be administered with caution in elderly individuals, who may be at greater risk for developing adverse reactions after epinephrine administration [*see WARNINGS AND PRECAUTIONS (5.4), OVERDOSAGE (10)*].

10 OVERDOSAGE

Overdosage of epinephrine may produce extremely elevated arterial pressure, which may result in cerebrovascular hemorrhage, particularly in elderly patients. Overdosage may also result in pulmonary edema because of peripheral vascular constriction together with cardiac stimulation. Treatment consists of rapidly acting vasodilators or alpha-adrenergic blocking drugs and/or respiratory support.

Epinephrine overdosage can also cause transient bradycardia followed by tachycardia, and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (prefibrillation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug such as propranolol.

Overdosage sometimes results in extreme pallor and coldness of the skin, metabolic acidosis, and kidney failure. Suitable corrective measures must be taken in such situations.

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Clinical GBS is characterized by muscle pain and symmetric, ascending paresis with minor sensory abnormality. The neurologic deficit of GBS progresses over several days to a month. In most cases, GBS develops 2 to 4 weeks after a prodromal gastrointestinal or respiratory illness or immunization. The history may include antecedent trauma or surgery. The contribution of influenza to GBS rates is not fully understood. Epidemiologic data suggest that there is a temporal association between influenza and developing GBS within 30 to 60 days.[7,26] The pathophysiology of GBS is not completely understood either; autoimmune phenomena can lead to damage of peripheral nerves causing muscle weakness.[27] There is no confirmatory laboratory test for GBS.

Diagnosis of influenza-associated neurologic complications

Despite extensive testing, it is not easy to establish causality between influenza virus infection and many of these neurologic conditions. Some of the conditions described here have similar clinical presentations, so the physician must differentiate among infectious, postinfectious (mediated by immunologic response), or noninfectious (eg, vasculitis) origin to guide patient management. Identifying an etiologic agent early in the course of the disease can be important for prognosis, potential prophylaxis, counseling of patients and family, and public interventions. Direct diagnostic workups help to rule in or exclude the most common etiologies.

Because CSF and neuroimaging findings are often unremarkable in patients with influenza-associated neurologic disease, the final diagnosis is based on clinical assessment of the neurologic manifestations and laboratory confirmation of acute influenza virus infection. During influenza outbreaks in the community, physicians should consider influenza in the differential diagnosis of patients with seizures and altered mental status, especially if patients developed respiratory signs and symptoms shortly before the onset of neurologic manifestations and even if a rapid influenza diagnostic test is negative. Rapid influenza tests provide results within 15 minutes or less, but the low sensitivity of these tests precludes the exclusion of influenza based on a negative result.[28]

Respiratory signs and symptoms caused by influenza virus infection overlap with those caused by other respiratory pathogens.[29] Moreover, young children are less likely to experience "typical" influenza symptoms (eg, fever and cough).[30] The best way to diagnose influenza is by the detection of viral RNA by reverse transcriptase polymerase chain reaction (RT-PCR) or by viral culture from upper respiratory tract specimens collected as close to illness onset as possible.[31] Serologic testing (antibody detection) is not recommended for routine diagnosis. Preferred respiratory samples for influenza testing include nasopharyngeal or nasal swab, and nasal wash or aspirate, depending on which type of test is used (Table 2).[32,33] Early diagnoses of influenza in patients with neurologic complications provide the option of using influenza antiviral therapy.

Treatment of influenza-associated neurologic complications

In general, immediate medical care is aimed at appropriate management of the airway, bladder function, fluid and electrolyte balance, nutrition, secondary pulmonary infection, and hyperpyrexia. Care in an ICU setting may be required, especially if seizure activity is sustained or intracranial pressure is increased. Encephalopathy/encephalitis is a neurologic emergency for which consultation with a neurologist is recommended; consultation with an infectious disease specialist is also appropriate. Guidelines on the management of encephalitis have been published recently and offer etiology-specific treatment recommendations.[34]

No study has evaluated whether treatment with influenza antiviral drugs can influence the course of influenza-associated neurologic complications. However, randomized, controlled trials have shown a reduction in the duration and severity of uncomplicated influenza in otherwise healthy children treated with neuraminidase inhibitors, and observational studies have shown a reduction in hospital stay among treated children admitted to the ICU with influenza.[35,36] Based on currently available data, prompt antiviral treatment is recommended for persons with severe influenza or those at risk of complications.[37] Although antiviral drugs work best when given within 48 hours of illness onset, observational studies have shown that treatment up to 5 days after

TABLE 2 Influenza virus testing methods

Method	Types detected	Acceptable specimens	Test time	CLIA waived
Viral cell culture (conventional)	A and B[a]	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 d	No
Rapid cell culture (shell vials; cell mixtures)	A and B[a]	As above	1-3 d	No
Immunofluorescence, direct (DFA) or indirect (IFA) antibody staining	A and B[a]	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 h	No
RT-PCR[b] (singleplex and multiplex; real-time and other RNA-based) and other molecular assays	A and B[a]	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	Varied (generally 1-6 h)	No[c]
Rapid influenza diagnostic tests[d]	A and B	NP swab (throat swab), nasal wash, nasal aspirate	<30 min	Yes/No

Abbreviations: CLIA, Clinical Laboratory Improved Amendments; DFA, direct immunofluorescence assay; IFA, indirect immunofluorescence assay; NP, nasopharyngeal; RT-PCR, reverse transcriptase polymerase chain reaction.
[a]May be adapted for identification of specific subtypes.
[b]Including FDA-approved test systems, reference laboratory testing using analyte-specific reagents or laboratory-developed reagents.
[c]Random-access, single-cartridge tests may be moderately complex.
[d]Immunochromatographic lateral flow and membrane-based immunoassays.
From Centers for Disease Control and Prevention[32] and Leland DS, et al.[33]

illness onset was associated with reduced morbidity and mortality among hospitalized patients. Current treatment guidelines are applicable to children.

The neuraminidase inhibitors oseltamivir (Tamiflu; Roche Laboratories; Nutley, New Jersey) and zanamivir (Relenza; GlaxoSmithKline; Research Triangle Park, North Carolina) are the only antiviral medications routinely recommended for treatment of influenza virus infection.[37] Antiviral resistance to oseltamivir and zanamivir among strains of influenza viruses expected to circulate during the 2013-2014 season is likely low. However, clinicians should monitor susceptibility information throughout the season either at the American Academy of Pediatrics Web site (http://www.aap.org or http://aapredbook.aappublications.org/flu) or the Centers for Disease Control and Prevention (CDC) Web site (http://www.cdc.gov/flu/index.htm).

Oseltamivir is available in capsule and oral-suspension formulations. The manufactured liquid formulation has a concentration of 6 mg/mL. If the commercially manufactured oral suspension is not available, retail pharmacies may open the capsule and mix the contents with a sweetened liquid to a final concentration of 15 mg/mL. Table 3 shows the recommended dosage and schedule for the treatment of influenza in children.[37,38] Information on influenza antiviral dosages and formulations is available at the CDC Web site: http://www.cdc.gov/flu/professionals/antivirals/index.htm.

Summary

Influenza remains a major cause of medically attended respiratory illness in young children. The most effective way to prevent influenza-associated neurologic complications is to prevent influenza. Annual influenza vaccination for children aged 6 months or older is recommended.[39] To protect children aged younger than 6 months, annual influenza vaccination of pregnant women and of those in close contact with young infants should be emphasized.

Multiple influenza vaccines are expected to be available during the 2013-2014 influenza season. In general, there will be trivalent and quadrivalent inactivated influenza vaccines (IIV3/IIV4) that are available in an intramuscular formulation and an intradermal formulation licensed for those aged 18 years and older; and a quadrivalent live attenuated influenza vaccine (LAIV4), which is given as an intranasal spray and can be used in healthy people aged 2 to 49 years.[39]

Influenza has been associated with a variety of neurologic complications of varying severity in children, such as febrile seizures, encephalopathy/

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Reference: 1. Data on file, Abbott Nutrition 2013.

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encephalitis, and GBS. Pediatricians must be aware of the appropriate diagnosis and treatment of influenza-associated neurologic findings and administer influenza vaccine according to current guidelines. CP

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TABLE 3 Recommended dosage and schedule of influenza antiviral medications in children

Antiviral agent[a]	Indication	Age group (in years)			
		0-6	7-9	10-12	≥13
Zanamivir	Treatment, influenza A and B	NA	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
Oseltamivir[b]	Treatment, influenza A and B	Dose varies by child's weight[c]	Dose varies by child's weight[c]	Dose varies by child's weight[c]	75 mg twice daily

Abbreviation: NA, not applicable.

[a] Zanamivir is manufactured by GlaxoSmithKline (Relenza; inhaled powder). Zanamivir is approved for treatment of persons aged ≥7 years and approved for chemoprophylaxis of persons aged ≥5 years. Zanamivir is administered through oral inhalation using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device. Zanamivir is not recommended for those persons with underlying airway disease. Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu; tablet). Oseltamivir is approved for treatment or chemoprophylaxis of persons aged ≥1 year. Oseltamivir is available for oral administration in 30-mg, 45-mg, and 75-mg capsules and liquid suspension. Oseltamivir is approved for treatment of persons aged ≥2 weeks.

[b] Recommended duration for antiviral treatment is 5 days. Longer treatment courses can be considered for patients who remain severely ill after 5 days of treatment.

[c] The treatment dosing recommendation for oseltamivir for children aged 2 weeks to <1 year is 3 mg/kg twice a day, and for those aged ≥1 year who weigh ≤15 kg is 30 mg twice a day. For children who weigh >15 kg and up to 23 kg, the dose is 45 mg twice a day. For children who weigh >23 kg and up to 40 kg, the dose is 60 mg twice a day. For children who weigh >40 kg, the dose is 75 mg twice a day.

From Fiore AE, et al[37] and US Food and Drug Administration.[38]

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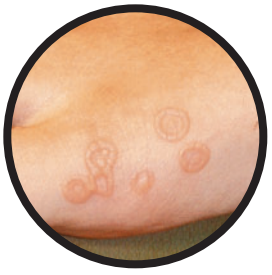
Foot rings in a 10-year-old girl



DIANE KUHN, MA, PHD, MS1, AND JIAWEI ZHAO, BS, MS1

THE CASE

You are asked to evaluate a 10-year-old girl for peculiar annular eruptions on her hands and feet following treatment for warts 6 weeks ago. What could be causing these eruptions?

FIGURE

Annular eruption on the patient's right great toe after 6 weeks of wart treatment.

DIAGNOSIS:

Ring warts secondary to treatment with cantharidin

CLINICAL FEATURES

Warts are common viral infections of the skin caused by human papillomavirus (HPV). There are over 100 types of HPV, and the type and anatomic site determine morphology.[1] Common warts (associated with HPV 1, 4, 27, 57)[2] typically present as rough hyperkeratotic papules with an irregular border.[3] They most often occur on the dorsal part of the hand or palm, but can appear on any part of the body.[4] Flat warts (associated with HPV 3 and 10)[2] are flat or slightly elevated flesh-colored lesions that are typically between 2 mm and 5 mm, and may be found in groups of anywhere from a few to dozens or more. They often present on the hands, knees, and shins. Plantar warts (associated with HPV 1)[5] occur on the plantar aspect of the foot, and can present with multiple lesions that, if contiguous, can form a thick keratotic plaque.[4] HPV is spread through skin-to-skin contact or through contaminated surfaces or objects.[6] It infects the basal keratinocytes of cutaneous and mucosal epithelium to produce proliferative lesions at these sites that we recognize clinically as warts.

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NATURAL HISTORY

HPV can have a long incubation period. One study on anogenital warts showed that the incubation period could vary from weeks to months, with an average of 3 months.[7] Nongenital warts are generally harmless and resolve spontaneously within months to years, with a two-thirds remission at 2 years in immunocompetent individuals.[8] Intact innate and cellular immunity are important in the regression of warts. Acquired antibodies play a role in the containment and reduction of HPV infectivity.[9] Also, antibodies provide immune surveillance to prevent future infection from HPV.[10]

EPIDEMIOLOGY

Warts are among the most common presenting complaints in pediatric dermatology.[6] According to 1 study, about one-third of schoolchildren have warts, with risk increased by the presence of affected family members or classmates.[11] Another study found that between 5% and 10% of pediatric patients had warts.[12] The peak incidence for warts in children is between the ages of 12 and 16 years. Although most wart-related cases are self-limited, patients frequently seek treatment in the meantime. One explanation could be that some patients with warts report considerable morbidities, particularly frustration and embarrassment.[13]

COMMON TREATMENTS AND OUTCOMES

Salicylic acid

Salicylic acid is a colorless organic acid that acts as a keratolytic agent. It destroys virally infected epidermis by reducing cohesion between corneocytes.[14] It is also an irritant that activates an immune response to help eliminate HPV.[15] Salicylic acid is available in many preparations and concentrations, but none has shown superiority over the others.[16] A meta-analysis of 6 trials of salicylic acid (with or without additional lactic acid) in the treatment of cutaneous warts showed that salicylic acid was superior to placebo in eliminating warts with efficacy ranging from 0% to more than 80%.[2] Adverse events include 1 cellulitis case in a trial of 29 participants and minor skin irritations that were occasionally reported in some of these other trials.

Cryotherapy

Cryotherapy, usually with liquid nitrogen, is a freezing process that destructs the warts by damaging cells and their vascular supply, and by stimulating the immune system.[2] A meta-analysis of 3 trials showed no advantage of cryotherapy over placebo. However, meta-analysis of 4 studies of 707 subjects comparing salicylic acid and cryotherapy showed no significant difference in the cure rate of warts between the 2 treatments, and salicylic acid has been shown to be more effective than placebo. Cure rates varied from 9% to 50% in randomized trials. There are no differences in the long-term cure rates between different treatment intervals of 2, 3, or 4 weeks. The probability of being cured is inversely related to the diameter of the largest wart and the length of history.[17] Adverse events from cryotherapy include pain, blistering, pigmentation of skin,[18] tendon or nerve damage with aggressive therapy, and onychodystrophy in the treatment of periungual warts.[19]

Cantharidin

Cantharidin is a vesicant made from extracts of beetles belonging to the order of Coleoptera and the family of Meloidae.[20] Cantharidin is absorbed by the lipid membranes of epidermal cells, causing the activation or release of serine proteases. This leads to the disintegration of the desmosomal plaque, resulting in detachment of tonofilaments from desmosomes. The process gives rise to acantholysis and intraepidermal blistering.[21] Topical treatment causes blistering after 24 hours to 48 hours of application.[20] The extent of blistering is limited by washing the treatment site with soap and water after a specified length of time.

Cantharidin was first suggested as a treatment for warts by Epstein and Kligman in 1958,[22] and has

CONTINUED ON **PAGE 50**

HEAD LICE
MYTHS, FACTS, TREATMENTS

FAST FACT Head lice have nothing to do with socioeconomic status, cleanliness, or hygiene.[1,2,3,4,5]

Back to school means saying hello to *Pediculus humanus capitis*—head lice. This special section reveals all you need to know about the creepy little critters and how you can help families rid their children of the infestation and the social stigma.

School is right around the corner, and so is the next influx of families with children who have contracted head lice—*Pediculus humanus capitis* (*P humanus capitis*). The critters pose no health hazard, are not a sign of poor hygiene, and, unlike body lice, do not spread disease.[1,2] The greatest injuries that head lice cause seem to be the social stigma and anxiety they harbor.

According to the American Academy of Pediatrics (AAP), infestations are common among children aged 3 to 12 years.[1] Head lice occur regardless of socioeconomic status or hygienic living conditions and are common in many parts of the world, with an incidence in school children ranging from 2% to 52%. The Centers for Disease Control and Prevention (CDC) estimates that, in the United States, there are 6 million to 12 million infestations each year in this group.[2] Interestingly, African Americans are less likely to play the unwilling host than are most other races, possibly because lice claws are less well adapted to grasping the shape and width of this type of hair shaft.

Head lice aren't particularly mobile. They can't fly or hop.[2] They need help getting from 1 host to the next. Specifically, they need direct head-to-head contact—the type of contact common in schools, sleepovers, slumber parties, camps, and sports activities—that typically occurs among kids. Much less common is transmission via clothing, bedding, or sharing hairbrushes or combs. Because lice feet are adapted to holding onto human hair, they have a hard time getting (and keeping) a grip on plastic, metals, leather, and similar materials.

A sordid history

Societal panic and stigmatization of head lice is not new. Although head lice's ancient lineage predates modern *Homo sapiens* by some 1.18 million years,[6] once louse and man joined up, they stayed that way. Strands of hair from an early historic Wyoming mummy revealed evidence for the presence of *P humanus capitis*,[7] and another study illustrates lice going to people's heads about 170,000 years ago.[8]

FAST FACT Head lice are tiny, wingless, live close to the human scalp, and feed on blood. The life cycle includes nits (eggs), nymphs (baby), and louse (adult). The nits are tiny, teardrop-shaped eggs attached to the hair shaft near the scalp. They hatch into nymphs, which grow into adults in 1 to 2 weeks. Grayish or white, adults are the size of sesame seeds.[5]

Of nits and stigmas

The stigma took a little longer to catch on, but it's tenacious. In the mid-1700s, sentiments expressed by Robert Burns—that lice were disgusting, the well-to-do should be protected from them, and the poor deserved them—were pervasive.[9] In the mid-1800s, lice infestations netted men 6 lashes with a cat-o'-nine-tails.[10]

Contemporary estimates are that 6 million to 12 million cases of head lice occur each year in the United States in children aged 3 to 12 years.[11] In an effort to curtail the spread of the parasites, Canada, Australia, and the United States implemented "no-nit" policies that entailed the immediate dismissal of all children with head lice, eggs, and/or nits from schools, camps, or child care settings.[13] However, because only a small number of children with nits on their hair are also infested with living lice, this policy did little to stem the spread of the parasite, but much to spread fear and confusion.

TABLE 1 The myths vs the facts

Myths	Facts
Only dirty people get lice.[a,b,c]	Hygiene and household or environment cleanliness are not factors in infestation.[a,b,c]
Lice carry disease.[b,c,d,e]	Lice do not spread diseases.[b,c,d,e]
Head lice can jump and fly and live anywhere.[c,f]	Head lice can only crawl and live only a day or 2 away from the human head.[c,f]
Home remedies such as mayonnaise get rid of lice.[c]	There's no evidence that home remedies are effective.[c]
Nits mean lice.[f]	Only a small number of children with nits are infested with live adult lice. The nits could be empty egg casings.[f]

[a]Frankowski BL, et al.[1]
[b]Centers for Disease Control and Prevention.[2]
[c]National Association of School Nurses.[5]
[d]American Academy of Pediatrics.[12]
[e]CNN Health.[4]
[f]Mumcuoglu KY, et al.[13]

TABLE 2 Treatments for head lice

Pharmaceutical/Chemical[a,b,c,d]	Manual/Nonpharmaceutical[d,e,f]
Over-the-counter medications: • Pyrethrins combined with piperonyl butoxide • Permethrin lotion, 1% **Prescription medications:** • Benzyl alcohol lotion, 5% • Ivermectin lotion, 0.5% • Malathion lotion, 0.5% • Spinosad 0.9% topical suspension **For second-line treatment only:** • Lindane shampoo, 1%	• Conditioner and comb or wet comb. • Daily use of nit combs with long metal teeth. Metal flea combs found in pet stores work well, too. • Manual removal of nits from hair shafts with fingernails. • Buzz-cut close haircut. • Employ professional nitpicker.

[a]Centers for Disease Control and Prevention.[2]
[b]Mumcuoglu KY.[14]
[c]Zuniga R, et al.[15]
[d]CNN Health.[4]
[e]Handbook of Non Drug Intervention (HANDI) Project Team.[16]
[f]American Academy of Pediatrics.[17]

It also made a serious annual dent in the economy, costing $4 billion to $8 billion in missed workdays for parents needing to stay home with their children.

FAST FACT One louse can live up to 30 days on the head, but dies within a day or 2 of falling off, and nits cannot hatch at temperatures lower than near the scalp. Short "off-scalp" survival is why transmission via clothing or hats is much less common than direct head-to-head contact, and why sealing items in plastic bags for 2 weeks kills any lice on the items.[1,2,4,12]

Assessing the damage

These policies—established years ago and based on fear and misinformation rather than scientific evidence—are formulated on a parasite that transmits no diseases to humans and that has nothing to do with poor hygiene or a sanitary home environment.[2,11,18] Close, head-to-head contact is the primary method of transmission.[2] It's easy to see how fear, anxiety, and psychological trauma can be the worst part of a head lice diagnosis.

Researchers have found that parents and caregivers of infected children suffer the consequences as well, often feeling ostracized, losing self-integrity, struggling with persistence of infection, and having difficulty managing strain.[19] Another study noted the negative social effects of the head lice stigma as more problematic than the infection itself, including quarantine, overtreatment, and potentially negative psychological impact.[20] Innocuous and unhealthy home remedies, such as the use of flammables or pesticides, were common, reflecting the confusion of parents who blamed head lice as the cause of various health problems not related to the insect.[21]

FAST FACT Dogs, cats, and other pets don't contribute to the spread of lice.[2]

Treatments: archaic and contemporary

Treatment for head lice ranges from the archaic—manual removal and home remedies—to the pharmaceutical and mechanical.[3,14,16,22] Before the advent of modern applications, people improvised with what was available, from date flour in the 16th century BC to later use of quicksilver, cresol, naphthalene, sulphur, mercury, kerosene, oil, and vinegar.[14]

FAST FACT Hot water (130°F) and heat drying kill lice, nits, and nymphs.[23]

While effective, insecticides have been met with evolution of pesticide-resistant strains of parasites, which has mandated strategic combinations and sequencing of product application.[3,14] Topical permethrin remains the first-line treatment, although permethrin-resistant strains can complicate its efficacy.[15] If 2 applications of permethrin are ineffective, topical application of malathion or ivermectin and even the off-label use of oral ivermectin may be indicated.

This tendency of the little parasites to evolve drug resistance makes their effective manual removal, plus education of parents on lice biology and control, all the more important for managing infestation and preventing reinfestation.[16,22]

Myths and facts

For all the stigma, fear, and psychological trauma they cause, head lice are actually pretty delicate, high-maintenance critters. A quick look at the myths and facts can set the record straight, and shift the power differential away from the parasites.

Head lice favor all socioeconomic groups and make themselves at home regardless of the health, hygiene, or cleanliness of their unwilling hosts. They don't spread disease. Really, all they do is create a disproportionate brouhaha, and their stigma is far worse than their bite. One of the worst effects of a head lice infestation is the psychological trauma that goes along with the diagnosis.

Knowledge is power, and this is certainly true where *P humanus capitis* is concerned. Educating parents and children about head lice myths and facts is key to demystifying the stigma. If pediatricians and school officials react calmly, parents can focus on treatment without the drama.[1] cp

FAST FACT Kill any hangers-on by soaking combs, barrettes, brushes, hair bands, and other hair goods in rubbing alcohol or Lysol for 1 hour.[23]

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TABLE 3 Best practice guidelines

Centers for Disease Control and Prevention[a]

Treat the infested person(s):

- Use an over-the-counter or prescription medication.
- Apply lice medicine according to the instructions contained in the box or printed on the label. If the infested person has very long hair (longer than shoulder length), it may be necessary to use a second bottle. Pay special attention to instructions on the label or in the box regarding how long the medication should be left on the hair and how it should be washed out.
- Have the infested person put on clean clothing after treatment.
- If a few live lice are still found 8-12 h after treatment, but are moving more slowly than before, do not retreat. The medicine may take longer to kill all the lice. Comb dead and any remaining live lice out of the hair using a fine-toothed nit comb.
- If, after 8-12 h of treatment, no dead lice are found and lice seem as active as before, a different pediculicide should be prescribed.
- Use nit combs to comb nits and lice from the hair shaft. Many flea combs made for cats and dogs are also effective.
- Checking hair and combing with a nit comb every 2-3 d after treatment may decrease the chance of self-reinfestation. Continue to check for 2-3 wk to be sure all lice and nits are gone. Nit removal is not needed when treating with spinosad topical suspension.
- Some drugs require routine retreatment about a week after the first treatment, others only if crawling lice are seen during this period. Retreatment with lindane shampoo is not recommended.

Supplemental measures:

- Machine wash and dry clothing, bed linens, and other items that the infested person wore or used during the 2 d before treatment using the hot water (130°F) laundry cycle and the high heat drying cycle.
- Clothing and items that are not washable can be dry-cleaned or sealed in a plastic bag and stored for 2 wk.
- Soak combs and brushes in hot water (at least 130°F) for 5-10 min.
- Vacuum the floor and furniture. However, the risk of getting infested by a louse that has fallen onto a rug or carpet or furniture is very small. Head lice survive less than 1-2 d if they fall off a person and cannot feed; nits cannot hatch and usually die within a week if they are not kept at the same temperature as that found close to the human scalp.
- Do not use fumigant sprays; they can be toxic if inhaled or absorbed through the skin.

American Academy of Pediatrics[b]

- No healthy child should be excluded from or miss school because of head lice. Because head lice are usually transmitted by head-to-head contact, parents should carefully check a child's head before and after sleepovers or camps where children share sleeping quarters.
- 1% permethrin lotion is recommended as initial treatment for most head lice infestations with a second application 7-10 d after the first. Parents and caregivers should make sure that any treatment chosen is safe; preferred treatments would be those that are easy to use, reasonably priced, and proven to be nontoxic. All products must be used exactly according to manufacturer's instructions.

National Association of School Nurses[c]

- Management of pediculosis should not disrupt the educational process. The school nurse's goals are to facilitate an accurate assessment of the problem, contain infestation, provide appropriate health information for treatment and prevention, prevent overexposure to potentially hazardous chemicals, and minimize school absence.
- Treatment recommendations for pediculosis should be based on evidence-based literature from public health, medical, and nursing content experts, although no pediculicide is 100% ovicidal, and resistance has been reported with lindane, pyrethrins, and permethrin.

[a]Centers for Disease Control and Prevention.[2]
[b]Frankowski BL, et al.[1]
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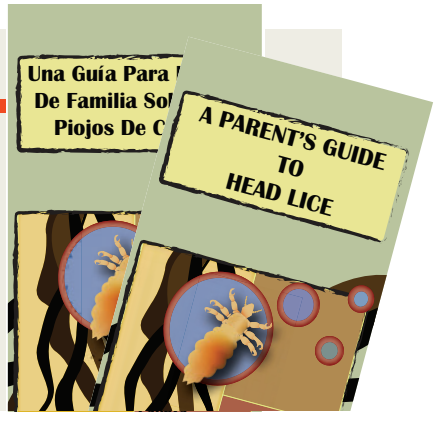
FAST FACT It may take 8 to 12 hours for a louse to die after treatment.[18]

RESOURCES FOR PARENTS

Download these helpful PDFs for your patients' families to take home:

A Parent's Guide to Head Lice (English)
http://www.cdph.ca.gov/HealthInfo/discond/Documents/2012HeadLiceEng.pdf

A Parent's Guide to Head Lice (Spanish)
http://www.cdph.ca.gov/HealthInfo/discond/Documents/2012HeadLiceSpa.pdf



The high-tech practice of the (near) future

Medical devices and technologies once portrayed in the realm of science fiction are finding their way into today's pediatric practice, and more are on the way.

The Pediatrics V2.0 articles published so far have detailed how technology can enhance office efficiency, expedite diagnoses, and improve patient care. Because there are many exciting medical technologies now in development, I thought it would be fun to discuss the gadgets and gizmos that may be part of the high-tech practice just a few years from now.

As consumers we have very high expectations regarding technologies we choose to be part of our daily lives. After all, we currently purchase 3-D high-definition TVs, cars with voice-controlled audio and navigation systems, and robots that keep our floors clean. What wonderful devices might be in the offing for pediatric practice just beyond the bend in the road? If you are curious, look through my crystal ball to see what technologies pediatricians will routinely use in the near future.

Better electronic health care records (EHRs)

The road to adoption of EHRs has been rocky indeed. Not surprisingly, EHRs are extremely expensive, and involve a huge initial investment that can easily exceed $20,000 per provider. Few pediatricians are receiving incentive payments for EHR adoption under the Affordable Care Act (ACA), which requires pediatric practices to have 20% to 30% of their patients enrolled in Medicaid to qualify. However, if accountable care organizations (ACOs) come to dominate the marketplace, pediatricians may find it necessary to adopt a comprehensive EHR to document all the quality measures these organizations require.

Many pediatricians complain that EHRs reduce productivity and very few are specifically written for pediatric practices, so choices for our specialty are limited. It is reasonable to expect that EHRs will mature over the next few years and feature simplified interfaces, perhaps with inputting via touchscreen computers. Vital signs will be transmitted wirelessly to our EHRs from our thermometers, blood pressure cuffs, infant scales, and pulse oximeters, speeding the office visit considerably. Such wireless communication and EHR integration is available today with the

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Connex Integrated Wall System (Welch Allyn; Skaneateles Falls, New York).

Perhaps most importantly, our dependence on paper as the currency of information exchange will gradually vanish. There will be no school forms, excuse notes, or information sheets that will need to be printed. All will be transmitted electronically to a patient's secure health care portal, as well as to recipients designated by the patient, and can be transported via an encrypted health care card for backup when the Internet is not available. All referral notes from consultants will be transmitted directly into our EHRs, eliminating the need for time-consuming scanning of paper records. Best of all, insurance payments will be processed in minutes rather than weeks. And yes, all health care information will be secure. Since much of the communication between physician and patient will occur via patient portals or during electronic visits, offices will realize the enhanced productivity and efficiency associated with a true "paperless" office.

Many pediatricians complain that EHRs reduce productivity and very few are specifically written for pediatric practices, so choices for our specialty are limited.

Better immunizations

Our patients are immune to a number of life-threatening illnesses because of the many vaccines administered at health maintenance visits. Parents and pediatricians accept that vaccinations hurt, but wouldn't it be wonderful if our vaccines could be delivered *painlessly*. Imagine a pediatric office where kids are not fearful of routine visits, because the jab of the needle will be a thing of the past.

PharmaJet (Golden, Colorado) is a company I've written about many times in these technology articles. The company makes the spring-loaded, needle-free **PharmaJet** injection system, and immunizations delivered with its injectors are less painful compared with immunizations given with traditional needled syringes. Pantac Biosolutions (Ruggell, Liechtenstein) manufactures a laser system, the **Precise Laser Epidermal System (PLEASE)**, that delivers transdermal medication for dermatologic purposes such as keloid removal. The company is working on improving this painless technology to be able to deliver vaccines subcutaneously or intramuscularly. In addition, a prototype of a new system from engineers at the Massachusetts Institute of Technology uses magnets to propel precise quantities of liquids through skin at high velocity, achieving an almost pain-free injection. While still experimental, there is a good chance that this will be commercialized in the near future.

Still other researchers are looking at alternative methods of immunizations. One research group is producing patches with vaccine-coated micro needles that puncture the skin, and the vaccines are slowly absorbed subcutaneously. Clearly, much research needs to be done, but less painful immunizations are likely to be available for pediatric patients at some point in the foreseeable future.

Better point-of-care testing

Pediatricians arrive at diagnoses more expediently and use antibiotics more judiciously because of the many point-of-care (POC) tests we use routinely. We diagnosis strep pharyngitis, lead poisoning, respiratory syncytial virus, mononucleosis, influenza, and suspected urinary tract infections in minutes. But what does the future offer?

I routinely screen teenaged girls for anemia with my **Pronto-7** from Masimo (Irvine, California), and the company is hard at work at making this technology feasible for use in uncooperative younger children who are typically screened for anemia at 1 year of age. If you have diabetic patients in your practice, no doubt many are using insulin pumps for better control. Presently, devices are available from Medtronic (Minneapolis, Minnesota) that can continuously measure glucose

It has been shown that portable ultrasound is more accurate in diagnosing pneumonia in children compared with auscultation.

levels in interstitial fluid, communicating wirelessly with a paired insulin pump and reducing the number of finger sticks needed to optimize glycemic control. Most pediatricians are quite familiar with bilirubinometers that can be used to screen for significant jaundice in newborns via spectrophotometric measurements. Similarly, there are biosensors becoming available that can measure glucose levels using reflected light.

Another exciting method of diagnosing medical conditions is via analysis of exhaled breath. We have long had the ability to diagnose lactose intolerance by measuring the hydrogen and methane content of exhaled breath. Exhaled nitric oxide levels are used at some centers to diagnose and monitor asthma exacerbations because levels correlate with airway inflammation. What is in the offing is the ability to measure volatile organic chemicals (VOCs) in exhaled breath. With sensitivities in the parts per billion, devices that measure VOCs can be used to diagnose conditions such as tuberculosis, cancers, and metabolic problems, as well as respiratory infections.

Another innovative technology that will improve POC testing is a device that can collect 20 microliters of blood for analysis via a novel extraction process. This is the **Tap 20** from Seventh Sense Biosystems (Cambridge, Massachusetts), now in clinical trials. The Tap 20 uses micro needles to painlessly collect blood from the forearm. This product may be available by year's end.

While traditionally physicians diagnose pneumonia by auscultation with our stethoscopes, a mobile handheld ultrasound system called the **Vscan** is currently available from GE Healthcare (Cleveland, Ohio) for $8,000. Physicians can be trained in its use either online or by participating in live training sessions. It has been shown that portable ultrasound is more accurate in diagnosing pneumonia in children compared with auscultation. In a recent study, the sensitivity of the Vscan for detecting pneumonia was 92% compared with just 24% for auscultation.[1] Considering that the reimbursement for ultrasounds can exceed $100 per test, a pediatric practice could easily recoup its investment in a mobile Vscan device within a year's time. The Vscan may expedite diagnosis and reduce patients' exposure to x-rays, while facilitating appropriate antibiotic use.

Electronic visits will be routine

I believe that, in the near future, electronic visits (known as e-visits) will be routine practice. Computer webcams or video cameras integrated into tablets improve our ability to communicate with parents. Web conversations are superior to phone conversations because we can read a parent's body language during discussions and actually "see" the child that is the subject of the conversation. Remote devices will make it easy for parents to take a complete set of vitals at home, not just a temperature. Once insurance reimbursement issues have been resolved, e-visits will likely become extremely popular because these will facilitate more efficient and cost-effective triage practices. E-visits alone may be sufficient to discuss and resolve behavior problems, bed-wetting, common rashes, or situations when medication dosages need adjustments.

Because e-visits will be compensated (unlike phone calls between a pediatric practice and patients seeking advice), practices will be motivated to adopt this new method of health care delivery. E-visits are the house call of our future and the technologies of the future will make it possible for an on-call physician to work in the comfort of a home office.

"Star Trek" medicine in our future

The "holy grail" of high-tech medical care for many physicians is the tricorder used by Leonard "Bones" McCoy in the original *Star Trek* television series. For those non-Trekkers among our readers, Dr. McCoy injected medications with a needle-free hypospray and could diagnose all manner of conditions with his medical tricorder device just by scanning the patient.

Star Trek already predicted that, in the future, we would have cell phones and tablet computers. Because bioengineers have been extremely busy developing tiny sensors for remote diagnostics, the medical tricorder may soon be a reality. We now have diminutive sensors that enable continuous glucose-level monitoring subcutaneously (see above) and small sensors placed at the wrist can measure an accurate blood pressure. Our current repertoire of "magical" technologies already includes temporal artery thermometers, digital stethoscopes, pulse oximetry, transcutaneous bilirubinometers, and transcutaneous hemoglobin measurement devices. Given the current state of biotechnology and wireless communication, it is very possible that one device could eventually integrate many of these capabilities, creating a medical tricorder.

The XPRIZE Foundation (Playa Vista, California) is a nonprofit organization that designs and manages public competitions intended to encourage technological development that could benefit mankind. To stimulate research and development of a practical tricorder device, Qualcomm Corporation (San Diego, California) is sponsoring the Qualcomm Tricorder XPRIZE—a $10 million global competition to "stimulate innovation and integration of precision diagnostic technologies, making reliable health diagnoses available directly to 'health consumers' in their homes." (Visit http://www.qualcommtricorderxprize.org for information.) This competition will last more than 3 years and already there are over 280 entries.

Because of innovation and research . . . that will improve pediatric practice, we all can expect our patients to "live long and prosper."

One of the most intriguing tricorder-type devices now being developed is the **Scanadu Scout** (Scanadu; NASA-Ames Research Park, Moffett Field, California). This is a hockey puck-shaped device that when pressed to the forehead will determine a patient's heart rate, temperature, and pulse oximeter reading. Scanadu has raised more than $1.4 million in investments via crowd funding as of this writing, and plans on producing other devices that will perform urinalysis and screen for infectious diseases such as influenza and strep pharyngitis.

The future looks bright indeed . . .

I've been reporting on the evolution of medical technologies for more than 25 years and believe the best is yet to come. Watch this space for updates on the devices and technologies mentioned in this article as new information becomes available. Because of innovation and research leading to the introduction of new gadgets and gizmos that will improve pediatric practice, we all can expect our patients to "live long and prosper." CP

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CONTINUED FROM **PAGE 39**

since become one of the most widely used agents by pediatric dermatologists. Studies of cantharidin use for warts indicate that both researchers and clinicians consider the treatment to be effective and to have potential as a front-line therapy.[20,22-24] In addition to its well-documented use as a treatment for cutaneous warts, recent research has suggested that cantharidin might serve as an effective therapy for facial flat warts as well.[25] Among the reported adverse events associated with cantharidin use are pain or irritation, itching, or pruritus. While 1 study described these adverse events as "exceedingly rare,"[20] others have found them to be far more common.[22]

With a few exceptions,[20,26] ring warts have received little attention as a potential adverse event in cantharidin treatment of warts. It is important for pediatric dermatologists to be aware of the potential for this adverse event in cantharidin treatment of warts because ring warts have the potential to be both embarrassing and frustrating to patients.

OUR PATIENT

Our patient went home happy with treatment of salicylic acid. CP

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ANGELS ON EARTH

Commending everyday heroes for what they do

Diana came into the world blue and limp. Immediately, her pediatrician intubated her and gave her oxygen. When she was stable, x-rays were taken that showed an abnormal elevation of her diaphragm over the right side. The diaphragm is a muscle that separates the chest from the abdomen and is essential for breathing. When part of the diaphragm protrudes into the chest, a condition called eventration, the child cannot breathe properly and becomes blue from lack of oxygen. If oxygen deprivation continues for a few minutes, damage to the brain, heart, and other organs occurs.

Diana had a stormy course at the hospital in her infancy. She needed oxygen for 6 days, digoxin to stimulate her heart, intravenous fluids, and antibiotics. She slowly recovered, but the lack of oxygen had already damaged her brain. This caused weak muscles and poor sucking and swallowing. Doctors advised Diana's mother to stimulate her daughter's lips and mouth by offering baby formula and massage, which she did patiently so that Diana could suck better. Because there was no improvement, eventually Diana needed to be fed by a tube through her nose. Her mother became very adept in inserting the tube for feeding purposes.

As the weeks passed, the effects of Diana's brain damage became apparent. She could not swallow the formula properly, and when solid foods were tried, she choked. Consequently, she had very poor weight gain. Tests showed that Diana had gastroesophageal reflux, and eventually an operation to correct the reflux was performed. When the surgery did not help, a tube was introduced through Diana's abdominal wall into her stomach to facilitate feeding. Thus, to some extent, her feeding problem was resolved.

As the years passed, Diana developed dislocation of her hip and scoliosis. Despite these physical handicaps and mental disability, and with her mother's constant encouragement, Diana slowly learned to speak, first single words, then a few simple sentences with a drawl. Her apprehension in my office slowly vanished, giving way to smiles. I was happy to see her progress.

When Diana was 11 years old, one day, when coming out of the examination room, I saw her moving her hand in a peculiar way.

"What is she doing?" I asked her mother.

"Diana, show it to the doctor," her mother prompted.

Diana slowly made a fist of her left hand and extended her thumb. She gingerly smiled and said, "A." Then, ever so slowly, she extended her fingers and put her thumb across her palm and said, "B." I realized that Diana was proudly showing me the alphabet sign language she had learned. I was flabbergasted.

The Lord looks for angel volunteers who are willing to help developmentally disabled and physically handicapped children.

I was also amazed at her mother, who for 3 years, day after day, patiently taught Diana the sign language. Because of her persistent efforts, Diana improved little by little.

These mothers who strive day by day, against all odds, to improve the quality of life for their children with cerebral palsy or mental retardation are to be commended. In my view, they are all heroes.

The Lord looks for angel volunteers who are willing to help developmentally disabled and physically handicapped children. He asks those angels to come down to earth.

We call them mothers. CP

RAGHAVENDRA RAO, MD
Porterville, California

DR RAO is in private practice at Sequoia Family Medical Center in Porterville, California. He is an author, columnist, and a member of Porterville Writers Group.

PROFESSIONAL MESSAGES

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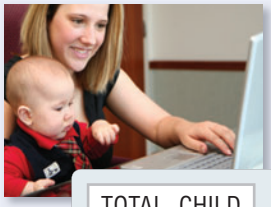

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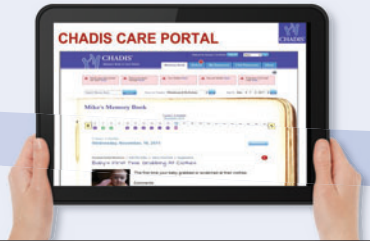

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CALENDAR

AUGUST

26-30: 19th Annual Pediatric Board Review Symposium. Cleveland, Ohio.
CONTACT: Cleveland Clinic, www.clevelandclinicmeded.com/live/courses/pediatric/overview.asp

SEPTEMBER

19-22: Pediatric Urology Fall Congress. Las Vegas, Nevada.
CONTACT: Society for Pediatric Urology, http://fallcongress.spuonline.org/

27-30: SDBP 2013 Annual Meeting. Baltimore, Maryland.
CONTACT: Society for Developmental and Behavioral Pediatrics, www.sdbp.org/annual_meeting.cfm

OCTOBER

11: Pediatric Nursing Conference. Pittsburgh, Pennsylvania.
CONTACT: Children's Hospital of Pittsburgh of UPMC, www.chp.edu/CHP/pediatric+nursing+conference

12-18: Aloha Update: Pediatrics 2013. Kauai, Hawaii.
CONTACT: Children's Hospital Los Angeles Medical Group, www.childrenshospitallamedicalgroup.org/site/c.pjK0KdMVKwG/b.4903949/k.9135/CME_Conferences.htm

15-16: Pediatric Neurorehabilitation Symposium 2013. Chicago, Illinois.
CONTACT: Rehabilitation Institute of Chicago, http://pediatric-nrs2013.com

23-26: 29th Annual Fall Conference on Pediatric Emergencies. Paradise Island, Bahamas.
CONTACT: Symposia Medicus, http://symposiamedicus.org/assets/conference/1273/1273.html

26-29: AAP National Conference and Exhibition. Orlando, Florida.
CONTACT: American Academy of Pediatrics, www.aapexperience.org

NOVEMBER

7-8: 22nd Annual Amazing Newborns Conference: Little Bugs, Big Hearts: Infectious Diseases of the Newborn and Congenital Heart Disease. Albuquerque, New Mexico.
CONTACT: University of New Mexico, Continuing Medical Education, www.medical-events.com/congress/22nd-annual-amazing-newborns-conference-little-bugs-big-hearts-infectious-diseases-of-the-newborn-and-congenital-heart-disease-2498

7-10: 7th Biannual Conference on Pediatric Sleep Medicine. Amelia Island, Florida.
CONTACT: Warren Alpert Medical School of Brown University, http://brown.edu/academics/medical/education/other-programs/continuing-medical-education/pedsleepmedconference

8-10: Southwest Regional NAPNAP Conference. Palm Springs, California.
CONTACT: National Association of Pediatric Nurse Practitioners, http://southwestregionalnapnapconference.com/

13-15: 30th Annual Colin J. Condron, MD, Care of the Sick Child Conference. Lake Buena Vista, Florida.
CONTACT: Orlando Health, Continuing Medical Education, www.orlandohealth.com/cme

DECEMBER

3-6: AANS/CNS Joint Section on Pediatric Neurosurgery 2013 Pediatric Section Meeting. Toronto, Canada
CONTACT: American Association of Neurological Surgeons/Congress of Neurological Surgeons, Section on Pediatric Neurological Surgery, http://pedsneurosurgery.org/meetings/current-meeting/

9-11: Hot Topics in Neonatology. Washington, DC.
CONTACT: Alfred I duPont Hospital for Children, www.hottopics.org/

20-21: 5th Annual Conference on Emergencies in Pediatrics. New York, New York
CONTACT: Symposia Medicus, http://symposiamedicus.org/Assets/Conference/1281/1281.html

HAVE AN EVENT?
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ADVERTISING INDEX

NATROBA™ (SPINOSAD) TOPICAL SUSPENSION, 0.9%

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NATROBA Topical Suspension safely and effectively.

Initial U.S. Approval: 2011

INDICATIONS AND USAGE

NATROBA Topical Suspension is a pediculicide indicated for the topical treatment of head lice infestations in patients four (4) years of age and older. (1)

DOSAGE AND ADMINISTRATION

- For topical use only. Not for oral, ophthalmic, or intravaginal use. (2)
- Shake bottle well. (2)
- Apply product to dry scalp and hair using only the amount needed to cover the scalp and hair. (2)
- Rinse off with warm water after 10 minutes. (2)

Repeat treatment if live lice are seen 7 days after first treatment. (2)

DOSAGE FORMS AND STRENGTHS

Suspension: 9 mg of spinosad per gram of NATROBA Topical Suspension. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Benzyl alcohol toxicity: Not recommended in infants below the age of 6 months; potential for increased systemic absorption. (5.1)

ADVERSE REACTIONS

Most common adverse events (>1%) were application site erythema and ocular erythema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ParaPRO, LLC at 1-855-628-7622 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Caution should be exercised when administered to a nursing mother. (8.3)

- Pediatric Use: Safety in pediatric patients below the age of 4 years has not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

PRESCRIBING INFORMATION FOR

NATROBA
(spinosad)
Topical Suspension
0.9%

1 INDICATIONS AND USAGE

1.1 Indication

NATROBA (spinosad) Topical Suspension is indicated for the topical treatment of head lice infestation in patients four (4) years of age and older.

1.2 Adjunctive Measures

NATROBA Topical Suspension should be used in the context of an overall lice management program:

- Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding and towels.
- Wash personal care items such as combs, brushes and hair clips in hot water.
- A fine-tooth comb or special nit comb may be used to remove dead lice and nits.

2 DOSAGE AND ADMINISTRATION

For topical use only. NATROBA Topical Suspension is not for oral, ophthalmic, or intravaginal use.

Shake bottle well. Apply sufficient NATROBA Topical Suspension to cover dry scalp, then apply to dry hair. Depending on hair length, apply up to 120 mL (one bottle) to adequately cover scalp and hair. Leave on for 10 minutes, then thoroughly rinse off NATROBA Topical Suspension with warm water. If live lice are seen 7 days after the first treatment, a second treatment should be applied. Avoid contact with eyes.

3 DOSAGE FORMS AND STRENGTHS

0.9%, viscous, slightly opaque, light orange-colored suspension.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Benzyl Alcohol Toxicity

NATROBA Topical Suspension contains benzyl alcohol and is not recommended for use in neonates and infants below the age of 6 months. Systemic exposure to benzyl alcohol has been associated with serious adverse reactions and death in neonates and low birth-weight infants [*See Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

NATROBA Topical Suspension was studied in two randomized, active-controlled trials (N=552) in subjects with head lice; the results are presented in Table 1.

Table 1: Selected Adverse Events Occurring in at least 1% of Subjects

Signs	Spinosad (N=552)	Permethrin 1% (N=457)
Application site erythema	17 (3%)	31 (7%)
Ocular erythema	12 (2%)	15 (3%)
Application site irritation	5 (1%)	7 (2%)

Other less common reactions (less than 1% but more than 0.1%) were application site dryness, application site exfoliation, alopecia, and dry skin.

Systemic safety was not assessed in pediatric subjects under 4 years of age as laboratory parameters were not monitored in these controlled studies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

There are no adequate and well-controlled studies with NATROBA Topical Suspension in pregnant women. Studies in humans did not assess for the absorption of benzyl alcohol contained in NATROBA Topical Suspension. Reproduction studies conducted in rats and rabbits were negative for teratogenic effects. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

No comparisons of animal exposure with human exposure are provided in this labeling due to the low systemic exposure noted in the clinical pharmacokinetic study [*see Clinical Pharmacology (12.3)*] which did not allow for the determination of human AUC values that could be used for this calculation.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 10, 50 and 200 mg/kg/day spinosad were administered during the period of organogenesis (gestational days 6 - 15) to pregnant female rats. No teratogenic effects were noted at any dose. Maternal toxicity occurred at 200 mg/kg/day. Oral doses of 2.5, 10, and 50 mg/kg/day spinosad were administered during the period of organogenesis (gestational days 7 - 19) to pregnant female rabbits. No teratogenic effects were noted at any dose. Maternal toxicity occurred at 50 mg/kg/day.

A two-generation dietary reproduction study was conducted in rats. Oral doses of 3, 10, and 100 mg/kg/day spinosad were administered to male and female rats from 10 - 12 weeks prior to mating and throughout mating, parturition, and lactation. No reproductive/developmental toxicity was noted at doses up to 10 mg/kg/day. In the presence of maternal toxicity, increased dystocia in parturition, decreased gestation survival, decreased litter size, decreased pup body weight, and decreased neonatal survival occurred at a dose of 100 mg/kg/day.

8.3 Nursing Mothers

Spinosad, the active ingredient in NATROBA Topical Suspension is not systemically absorbed; and therefore, will not be present in human milk. However, NATROBA Topical Suspension contains benzyl alcohol, which may be systemically absorbed through the skin, and the amount of benzyl alcohol excreted in human milk with use of NATROBA Topical Suspension is unknown. Caution should be exercised when NATROBA Topical Suspension is administered to a lactating woman. A lactating woman may choose to pump and discard breast milk for 8 hours (5 half-lives of benzyl alcohol) after use to avoid infant ingestion of benzyl alcohol.

8.4 Pediatric Use

The safety and effectiveness of NATROBA Topical Suspension have been established in pediatric patients 4 years of age and older with active head lice infestation [*see Clinical Studies (14)*].

Safety in pediatric patients below the age of 4 years has not been established. NATROBA Topical Suspension is not recommended in pediatric patients below the age of 6 months because of the potential for increased systemic absorption due to a high ratio of skin surface area to body mass and the potential for an immature skin barrier.

NATROBA Topical Suspension contains benzyl alcohol which has been associated with serious adverse reactions and death in neonates and low birth-weight infants. The "gasping syndrome" (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birthweight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants, as well as patients receiving high dosages, may be more likely to develop toxicity [*see Warning and Precautions (5.1)*].

8.5 Geriatric Use

Clinical studies of NATROBA Topical Suspension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

10 OVERDOSAGE

If oral ingestion occurs, seek medical advice immediately.

11 DESCRIPTION

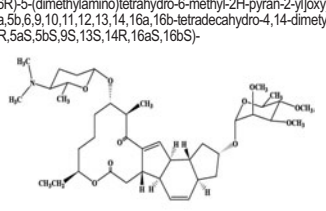
NATROBA (spinosad) Topical Suspension, is a slightly opaque, light orange colored, viscous topical suspension.

Spinosad, the active ingredient, is derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa.*

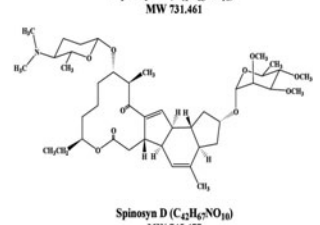
Spinosad is a mixture of spinosyn A and spinosyn D in a ratio of approximately 5 to 1 (spinosyn A to spinosyn D).

Spinosyn A: The chemical name is: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,a5-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-metyl-, (2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-

Spinosyn D: The chemical name is: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimetyl-, (2S,3aSR,5aS,5bS,9S,13S,14R,16aS,16bS)-



Spinosyn A ($C_{41}H_{65}NO_{10}$)
MW 731.461



Spinosyn D ($C_{42}H_{67}NO_{10}$)
MW 745.477

NATROBA Topical Suspension contains 9 mg spinosad per gram in a viscous, slightly opaque, light orange colored vehicle consisting of Water, Isopropyl Alcohol, Benzyl Alcohol, Hexylene Glycol, Propylene Glycol, Cetearyl Alcohol, Stearalkonium Chloride, Ceteareth-20, Hydroxyethyl Cellulose, Butylated Hydroxytoluene, FD&C Yellow #6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Spinosad causes neuronal excitation in insects. After periods of hyperexcitation, lice become paralyzed and die.

12.2 Pharmacodynamics

The pharmacodynamics of NATROBA Topical Suspension has not been studied.

12.3 Pharmacokinetics

An open-label, single-center study was conducted over a period of seven days to determine the pharmacokinetic profile of spinosad 1.8% in pediatric subjects with head lice infestation. Fourteen (14) subjects, 4 - 15 years of age, with head lice were enrolled into the study. All subjects applied a single topical (scalp) treatment of spinosad 1.8% for 10 minutes, after which the test article was washed off, and subjects underwent plasma sampling. Plasma samples were analyzed by a validated LC/MS/MS method. Results demonstrated that spinosad was below the limit of quantitation (3 ng/mL) in all samples. The bioavailability of benzyl alcohol from NATROBA Topical Suspension is unknown as plasma concentrations of benzyl alcohol were not determined in these subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of fertility

In an oral (diet) mouse carcinogenicity study, spinosad was administered to CD-1 mice at doses of 0.0025, 0.008, and 0.036% in the diet (approximately 3.4, 11.4, and 50.9 mg/kg/day for males and 4.2, 13.8, and 67.0 mg/kg/day for females) for 18 months. No treatment-related tumors were noted in the mouse carcinogenicity study up to the highest doses evaluated in this study of 50.9 mg/kg/day in male mice and 13.8 mg/kg/day in female mice. Female mice treated with a dose of 67.0 mg/kg/day were not evaluated in this study due to high mortality.

In an oral (diet) rat carcinogenicity study, spinosad was administered to Fischer 344 rats at doses of 0.005, 0.02, 0.05, and 0.1% in the diet (approximately 2.4, 9.5, 24.1 and 49.4 mg/kg/day for males and 3.0, 12.0, 30.1 and 62.8 mg/kg/day for females) for 24 months. No treatment-related tumors were noted in the rat carcinogenicity study in male or female rats up to the highest doses evaluated in this study of 24.1 mg/kg/day in male rats and 30.1 mg/kg/day in female rats. Rats in the highest dose group in this study were not evaluated due to high mortality.

Spinosad demonstrated no evidence of mutagenic or clastogenic potential based on the results of four in vitro genotoxicity tests (Ames assay, mouse lymphoma L5178Y assay, Chinese hamster ovary cell chromosome aberration assay, and rat hepatocyte unscheduled DNA synthesis assay) and one in vivo genotoxicity test (mouse bone marrow micronucleus assay).

Oral administration of spinosad (in diet) to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 10 mg/kg/day [*see Pregnancy (8.1)*].

14 CLINICAL STUDIES

Two multicenter, randomized, investigator-blind, active-controlled studies were conducted in 1038 subjects 6 months of age and older with head lice infestation. A total of 552 subjects were treated with NATROBA Topical Suspension. For the evaluation of efficacy, the youngest subject from each household was considered to be the primary subject of the household, and other members in the household were enrolled in the study as secondary subjects, and evaluated for all safety parameters.

In Study 1, 91 primary subjects were randomized to NATROBA Topical Suspension, and 89 primary subjects were randomized to permethrin 1%. In Study 2, 83 and 84 primary subjects were randomized to NATROBA Topical Suspension and permethrin 1%, respectively.

In both studies, all subjects who were treated on Day 0 returned for efficacy evaluation at Day 7. Subjects with live lice present at Day 7 received a second treatment. Subjects who were lice free on Day 7 were to return on Day 14 for evaluation. Subjects with live lice and who received a second treatment were to return on Days 14 and 21.

Efficacy was assessed as the proportion of primary subjects who were free of live lice 14 days after the final treatment. Table 2 contains the proportion of primary subjects who were free of live lice in each of the two trials.

Table 2. Proportion of Subjects Free of Live Lice 14 days After Last Treatment

Study 1		Study 2	
Natroba N=91	**permethrin 1% N=89**	**Natroba N=83**	**permethrin 1% N=84**
77 (84.6%)	40 (44.9%)	72 (86.7%)	36 (42.9%)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NATROBA (spinosad) Topical Suspension, 0.9% is a slightly opaque, light orange colored, viscous liquid, supplied in 4 oz. (120 mL) high density polyetheylene (HDPE) bottles. NDC 52246-929-04

16.2 Storage and Handling

- Store at 25˚C (77˚F); excursions permitted to 15˚ to 30˚C (59˚ to 86˚F).
- Keep out of reach of children

17 PATIENT COUNSELING/INFORMATION

[*See FDA-approved patient labeling (Patient Information)*]

The patient should be instructed as follows:

- Shake bottle well immediately prior to use
- Use NATROBA Topical Suspension only on dry scalp and dry scalp hair.
- Do not swallow.
- Avoid contact with eyes. If NATROBA Topical Suspension gets in or near the eyes, rinse thoroughly with water.
- Wash hands after applying NATROBA Topical Suspension
- Use NATROBA Topical Suspension on children only under direct supervision of an adult.
- If pregnant or breastfeeding, consult a physician before use.

Sections or subsections omitted from the full prescribing information are not listed.

Manufactured for ParaPRO LLC. Distributed by ParaPRO LLC and/or Pernix Therapeutics.

NAT-OPI-001 Effective Date: 27JUN2011 **Revised: 6/2011**

In two phase 3 clinical trials, nearly twice as many patients were free of head lice 14 days after final treatment with Natroba™ as compared to patients treated with Nix® (permethrin 1%) ~85% and 87% vs. ~45% and 43%, P<0.001.[1]

Please see reverse side for Prescribing Information and visit www.Natroba.com.

Natroba is available by prescription only.

www.Natroba.com

[1] Stough et al. *Pediatrics* 2009

NAT-PAD-001

Natroba™
(spinosad) Topical Suspension, 0.9%

Indication

Natroba Topical Suspension is a pediculicide indicated for the topical treatment of head lice infestations in patients four (4) years of age and older.

Adjunctive Measures

Natroba Topical Suspension should be used in the context of an overall lice management program:

- Wash (in hot water) or dry clean all recently worn clothing, hats, used bedding and towels
- Wash personal care items such as combs, brushes, and hair clips in hot water

A fine-toothed comb or special nit comb may be used to remove dead lice and nits.

Important Safety Information

Natroba Topical Suspension contains benzyl alcohol and is not recommended for use in neonates and infants below the age of 6 months. Systemic exposure to benzyl alcohol has been associated with serious adverse reactions and death in neonates and low birth-weight infants. Most common adverse events were application site redness (3%) and ocular redness (2%).