CONTEMPORARY PEDIATRICS JUNE 2013, VOL. 30 NO. 6 ELECTRONIC COMMUNICATION ■ GENETIC TESTING FOR INTELLECTUAL DISABILITY ■ MOBILE MEDICAL DEVICES ■ NEONATAL STUDIES

CONTEMPORARY Pediatrics®

JUNE 2013
VOL. 30 | NO. 6

Expert Clinical Advice for Today's Pediatrician

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Expert Clinical Advice for Today's Pediatrician

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PEER-REVIEWED ARTICLES

12 **E-communicating with adolescents in primary care**
Health care providers who see the potential of electronic media and understand health privacy issues may be ready to use these technologies for improving patient care.
Susan J Woolford, MD, MPH; Natalie Blake, MA; Sarah J Clark, MPH

21 **Genetic testing for intellectual disability**
Recent AAP guidance on genetic testing in children warrants pediatricians' awareness of the newest screening modalities.
Christa W Habela, MD, PhD
Ada Hamosh, MD, MPH

MYSTERIES & QUANDARIES

31 **DERMATOLOGY: WHAT'S YOUR DX?**
Black spots on a toddler's skin
Euphemia W Mu, MS IV
Brian C Capell, MD, PhD
Leslie Castelo-Soccio, MD, PhD

FOR YOUR PRACTICE

33 **PEDIATRICS V2.0 IMPROVING PATIENT CARE: SMARTPHONES AND MOBILE MEDICAL DEVICES**
Mobile medical gadgetry is in its infancy, yet these devices can help you motivate pediatric patients and their parents to adopt healthier lifestyles.
Andrew J Schuman, MD

DEPARTMENTS

NEWS & COMMENTARY

4 **GUEST EDITORIAL** Alternate vaccine schedules are not safer and should be obsolete. *Michael Brady, MD*

6 **YOUR VOICE**

7 **NEWS UPDATE**

11 **EYE ON WASHINGTON**
FDA subcommittee focuses on neonatal studies.

19 **JOURNAL CLUB**

IN ADDITION

1 **EDITORIAL ADVISORY BOARD**

38 **CLASSIFIEDS**

INSIDE BACK COVER **EVENTS CALENDAR**

INSIDE BACK COVER **AD INDEX**

Contemporary Pediatrics (Print ISSN: 8750-0507, Digital ISSN: 2150-6345) is published monthly by Advanstar Communications, Inc., 131 W. 1st Street, Duluth, MN 55802. Subscription rates: one year $89, two years $150 in the United States & Possessions, $105 for one year, $189 for two years in Canada and Mexico; all other countries $105 for one year, $189 for two years. Single copies (prepaid only) $18 in the United States; $22 in Canada and Mexico, and $24 in all other countries. Include $6.50 per order plus $2.00 per additional copy for U.S. postage and handling. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. POSTMASTER: Please send address changes to *Contemporary Pediatrics*, PO Box 6083, Duluth, MN 55806-6083. Canadian GST number: R-124213133RT001. Publications Mail Agreement Number 40612608. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, CANADA . Printed in the U.S.A.

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MICHAEL BRADY, MD

ALTERNATE VACCINE SCHEDULES ARE NOT SAFER AND SHOULD BE OBSOLETE

Since the days of Edward Jenner, the father of smallpox vaccine, there have been parents who have been vaccine hesitant, and at times vaccine refusers. After Benjamin Franklin's son died of smallpox, he lamented the fact that he had prohibited his son from getting the smallpox vaccine due to his concerns over safety.

Vaccines are no different than any other medical therapy. It is essential that patients or their parents make an informed decision whether to immunize. Fortunately, evidence supports the efficacy and safety of the vaccines currently recommended by the Advisory Committee on Immunization Practices (ACIP)[1] and the American Academy of Pediatrics (AAP).[2] Immunizations have been noted to be 1 of the 10 great public health achievements in the 20th century.[3] But still there are doubts.

The Institute of Medicine (IOM) has been very good at reviewing evidence and providing reports that have markedly enhanced our understanding of how to provide more effective and safer health care. The IOM is an independent, nonprofit organization that works outside the government to provide unbiased and authoritative advice to decision makers and the public.[4] In the past, the IOM has reviewed the safety of individual vaccines.[5] The 2012 IOM report has clearly delineated adverse events that are causally associated with vaccines. More importantly, IOM has reviewed scientific evidence to identify those adverse events that are not causally related to vaccines; eg, autism and the measles vaccine.

DR BRADY is physician-in-chief, Nationwide Children's Hospital, and professor of pediatrics, The Ohio State University, Columbus.

However, as the safety of individual vaccines became more evident, vaccine detractors started to target the vaccine schedule. As the number of vaccines increased over the past 2 decades, concern was raised that the number of vaccines given to children was unsafe, possibly overwhelming the ability of the child's immune system to manage such an antigen exposure. Despite a lack of biologic plausibility and ample preapproval studies refuting these concerns, vaccine-hesitant families were persuaded that "alternate vaccine schedules" that spaced the vaccines further apart would be better for their children.

IOM took on the task of reviewing the evidence concerning the currently approved vaccine schedule. Its report supporting the safety of the current vaccine schedule was recently released.[6] More importantly, IOM believes that it would not be appropriate to conduct studies of alternate schedules to the approved schedule if the alternate schedule delayed any of the vaccines and that any delay in vaccines would increase the period of risk for vaccine-preventable diseases. This increased risk for vaccine-preventable diseases would make these alternate schedules less safe (not safer) than the approved schedule.

The IOM report states that continued evaluation of vaccine safety is necessary to monitor for rare or unanticipated adverse events. IOM believes that the currently available surveillance systems such as the Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD), and postlicensure

studies conducted by vaccine manufacturers have been valuable in monitoring vaccine adverse events and providing timely information to inform vaccine policy.

Parents choose alternate vaccine schedules because they have concerns about vaccine safety and the increasing number of vaccines that their children receive. The ACIP/AAP-recommended immunization schedules were developed following significant research studies assessing their effectiveness and safety. None of the alternate schedules has been evaluated in this manner. Individuals who advise families to utilize alternate schedules capitalize on families' misperceptions and fears; however, their endorsements fall short in evidence.

The IOM report provides parents with 2 important pieces of information to inform their decision making: (1) Available evidence supports that the current vaccine schedule is safe and (2) any vaccine schedule that delays vaccines is less safe than the approved schedule because it places these children at risk of acquiring vaccine-preventable disease for a longer period of time.

Are alternate vaccine schedules obsolete? With this new report from IOM, they certainly should be. cp

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MEDICINE AS A CALLING

Our rewards are in proportion to our engagement.

I have been thinking recently of a special patient whom I cared for during my residency. It has been 13 years since this happened, but I remember it as if it were yesterday.

I was the intern on the pediatric inpatient ward rotation during February and March at a military clinic and hospital in the Pacific Northwest that served as a referral center for military dependents from bases in several states. I was finishing my third inpatient month in a row and feeling the effects of frequent overnight calls (before the 80-hour workweek) as well as seasonal affective disorder from 100 consecutive days of overcast skies and rain. I finally had a day off, and I was looking forward to lying around my apartment, catching up on opening my mail, paying bills in my pajamas, and taking a long nap. I needed a mental break from work, even if just for one day.

Around midday, my senior resident phoned me. She told me that our patient Anthony was asking for me to come in to be with him that day. I had known Anthony for more than a year. He was a 16-year-old boy with a tumor growing along his thoracic spine who had done chemo and radiation numerous times and had contemplated surgical excision. He was not given a good prognosis because of the extent of local spread of his tumor and the potential for paralysis from surgery or from more recent growth along the thoracic nerve outlets along his spine. Some neurosurgeons felt that the tumor was inoperable.

Anthony was becoming weaker and noting shortness of breath and paresthesia in his legs, trunk, and arms. He had a great family, a sweet girlfriend, and many friends who spent countless hours in his room sitting up at night with him on my many on-call nights. We talked about all kinds of things—how he felt about his tumor and treatments, his plans for the future, his fears. He had recently decided, after much discussion with his oncologist, neurosurgeon, and family, that he was not going to live paralyzed. He elected to have palliative care and enjoy what time he had left.

On this weekend, Anthony had a sense that the end was near. My senior resident explained that he didn't feel he had much time and he wanted to see me. At first, I just couldn't believe that I was going to get dressed and go back to the hospital. Yet I decided to go, and I spent the afternoon sitting with Anthony, his family, and his girlfriend. I fell asleep sitting up in the chair at one point. I don't think I fully appreciated what was going on with him, but he hugged me hard and thanked me for everything I had done to help him during his illness. I said good night and went home, falling into a very deep sleep as soon as I lay down.

I remember waking up around 4:30 AM and thinking, "Anthony's gone." I got up and showered, put on clean scrubs, and drove back to the hospital. He had indeed passed during his sleep without apparent discomfort or anxiety. I remember feeling as if my day off had been very different from what I had hoped, but so much more worthwhile than sitting around at home. I would have felt upset had I not gone to see him at his request and stayed the afternoon.

My experience with Anthony helped me many months later while I was caring for his younger brother, who was then having psychosomatic complaints and anxiety. It has helped me to remember the special opportunity we have as pediatricians to bond with and care for patients and their families. It has also helped me to remember that medicine is not a job but a calling.

Although practicing medicine may be inconvenient at times, the intangible rewards and learning are in proportion to our efforts and mental engagement, not how many hours we worked or had off. CP

CHARLOTTE M LEE, MD
Henderson, New York

DR LEE is a pediatrician, the mother of 4 children, and an Air Force spouse.

Pediatric subspecialists fail to follow guidelines for treating ADHD

More than 90% of pediatric subspecialists who diagnose and manage attention-deficit/hyperactivity disorder (ADHD) in young children deviate from current recommendations of the American Academy of Pediatrics (AAP) and the American Academy of Child and Adolescent Psychiatry regarding treatment of pediatric ADHD.

Clinical guidelines advise that preschoolers with ADHD receive initial treatment with behavior modification, followed by pharmacotherapy with the first-line medication methylphenidate when behavior modification is not successful.

Preliminary data from a survey of 560 board-certified pediatric subspecialists including developmental-behavioral pediatricians, child psychiatrists, and child neurologists revealed that just 8%, 12%, and 9%, respectively, complied with the clinical guidelines.

One in 5 respondents reported using medication as first-line treatment often or very often. Among all respondents who prescribed medication for initial treatment of pediatric ADHD, more than one-third reported choosing amphetamines or nonstimulants rather than methylphenidate. There were no differences across subspecialties regarding initiation of medication or selection criteria.

The researchers say it is unclear why so many clinicians who specialize in management of ADHD fail to comply with treatment guidelines.

Chung J, Sunday S, Meryash D, Gutman A, Adesman A. Medication management of preschool ADHD by pediatric sub-specialists: non-compliance with AAP clinical guidelines. Paper presented at: Pediatric Academic Societies Annual Meeting; May 2012; Washington, DC.

SUBLINGUAL DROPS EFFECTIVE AS INJECTIONS FOR ALLERGIES, ASTHMA

New research from Johns Hopkins Children's Center suggests that both under-the-tongue drops and injections work well to alleviate the symptoms of allergic rhinoconjunctivitis and asthma in children.

Investigators conducted a systematic review of 34 randomized, controlled clinical trials of children with asthma or rhinoconjunctivitis who were treated with either subcutaneous immunotherapy or an aqueous formulation of sublingual immunotherapy.

They first looked at 13 studies of 920 children that compared the effectiveness of allergy injections with standard allergy medication or placebo. Data showed that injections provided better symptom relief for asthma and allergic rhinitis than placebo or medication. Next, they analyzed 18 trials of 1,580 children who were treated with oral allergy drops, placebo, or medication for asthma and rhinitis or either condition alone. They found that oral drops were superior to placebo or medication in alleviating symptoms of asthma, allergic rhinitis, and rhinoconjunctivitis.

Researchers point out that sublingual immunotherapy is not yet approved for pediatric asthma and allergic rhinitis by the US Food and Drug Administration. The treatment is prescribed off-label in some clinical practices.

Kim JM, Lin SY, Suarez-Cuervo C, et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics*. 2013:131(6):1-13.

PRETERM INFANTS MAY NEED HIGHER DAILY INTAKE OF VITAMIN D

Preliminary data from a randomized, double-blind trial reveals that giving preterm babies daily supplementation of 800 international units (IU) of vitamin D reduces vitamin insufficiency that may lead to softening and weakening of their bones.

At 40 weeks, a group of preterm infants receiving 800 IU of vitamin D_3 showed lower insufficiency than a group receiving 400 IU (38% vs 67%, respectively) and the lower rate held at 3 months corrected age (12% vs 35%, respectively).

Despite improvement in serum vitamin D levels in the 800 IU group, dual energy x-ray absorptiometry at 3 months did not reveal better bone mineralization.

Natarajan CK, Sankar MJ, Agarwal R, et al. Daily vitamin D supplementation with 800 IU vs. 400 IU in preterm infants: a randomized trial. Paper presented at: Pediatric Academic Societies Annual Meeting; May 2013; Washington, DC.

What does Auvi-Q™ (epinephrine injection, USP) offer my patients at risk for anaphylaxis?

Audio and Visual Cues

Auvi-Q has voice instructions to guide users through the injection process and an LED light to alert them when the injection is complete.

Unique Size and Shape

Auvi-Q measures just 3 3/8" high, 2" wide, and 5/8" thick.

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

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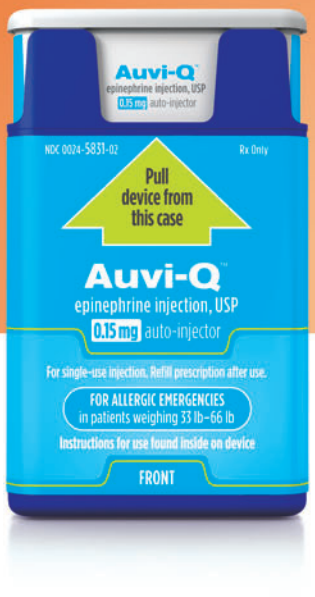

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Auvi-Q is the only epinephrine auto-injector that talks users step by step through the injection process. Visit auvi-q.com/hcp or scan the QR code below to watch the demo.

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0.15 mg for patients 33 lb - 66 lb

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Important Safety Information (continued)

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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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.

Revised September 2012

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EPI-BPLR-SA-SEP12

FDA subcommittee to examine regulatory science for neonatal studies

KATHRYN FOXHALL

The US Food and Drug Administration (FDA) is beginning its new effort to stimulate research on treatments for neonates in the wake of last year's legislation, the FDA Safety and Innovation Act.

An Institute of Medicine report last year said that from 1998 through 2010, only 23 (6%) of the 365 labeling changes that involved the submission of new pediatric studies "included the addition of information from studies with neonates."

A recent commentary on the subject of federal legislation and the advancement of pediatric drug studies said the lack of clinical trials on neonates implies they are a "therapeutic orphan," at potential risk for getting ineffective medications and invalidated doses, and for developing unanticipated complications including adverse drug reactions.

As part of the new work, in March the FDA held the first meeting of its neonatology subcommittee with 13 experts from government and clinical practice to discuss advancing the regulatory science.

Now the agency is moving toward bringing a senior level neonatologist into the FDA to help create a strategy, although it's too early to say whether that person can be on board soon, said Robert Nelson, MD, PhD, deputy director of the FDA's office of pediatric therapeutics, in an April interview.

Although Congress called for a neonatologist in that capacity, it did not provide funds for the position. However, the FDA says funding will be available through the Oak Ridge Institute for Science and Education for a fellowship for what will probably be part-time work for up to 2 years, "depending on the seniority of the candidate and the percent of effort dedicated to the fellowship."

Nelson said there's been interest expressed in the position. "We don't think that hiring just one neonatologist within FDA is going to solve the broader problem of trying to facilitate product development for the neonatal population," he said, so the agency also wants to leverage the expertise of the neonatal community.

That's one reason for the neonatal subcommittee, he said. The hope is that the agency will be able to reach out to individual neonatologists to work on specific issues, with the internal neonatologist being the point of contact.

Nelson said he hopes the person will be mid or late career and well placed within the neonatal community to get the process up and running.

A goal will be to make some "early wins" by identifying products or product areas in which progress can be made quickly. Perhaps demonstrating the value of the process would help the agency make an argument for funds to complete the congressional mandate to have a neonatologist for at least 5 years, he noted.

One challenge, said Nelson, will be getting studies done on the many drugs that are no longer under patent and that are being used off-label in neonatal intensive care units. Another challenge is getting industry to see neonatology as an area in which to develop new products for problems without adequate treatment.

One possibility being discussed, he said, is something similar to a public-private consortium to study the challenges to that research, including such things as lengths of trials and endpoints.

Jonathan Davis, MD, acting chair of the FDA neonatology subcommittee and chief of the division of newborn medicine at Tufts Medical Center in Boston, also pointed out that the legislation gives the agency more leverage to get drug companies to conduct research on neonates, unless there is a specific reason not to.

"There have been many instances, even in recent history, where we have finally studied the drug in great detail and found that it doesn't work [in newborns] or it may not be safe," he said. "It is something that we feel very strongly about, that we have to help babies, because if we don't, I am not sure who will," said Davis. CP

TEXTING, TWEETING, AND TALKING: E-COMMUNICATING WITH ADOLESCENTS IN PRIMARY CARE

SUSAN J WOOLFORD, MD, MPH; NATALIE BLAKE, MA; AND SARAH J CLARK, MPH

Health care providers who understand the potential of electronic media and associated health privacy and security issues may be ready to harness these technologies to improve clinical care for their teenaged patients.

With rapidly increasing access to mobile devices and the Internet, adolescents spend increasingly less time communicating in person and more time communicating electronically. Health care providers may be in a position to harness the power of novel mobile and electronic technologies to improve communication with adolescent patients and potentially enhance their health outcomes. In this article, we explore the role of electronic communication (e-communication) with teenagers, including the use of e-mail, text messaging, social media, and video chatting. Our objective is to highlight relevant issues to consider when deciding whether to incorporate e-communication into pediatric practice with adolescents.

Adolescents' use of e-communication

When considering the feasibility of e-communication with adolescent patients, it is helpful to know the forms they typically use. Some trends are identifiable, despite the fact that technology changes at lightning speed and what is acceptable to teenagers today versus what is "so yesterday" is a moving target.

E-mail—The vast majority of adolescents (92%) have Internet access, but e-mail is not their preferred means of communicating with social contacts.[1] It is unknown, however, whether e-mail might be considered acceptable for "business" purposes such as communicating with teachers, employers, or health care providers. In these interactions, teenagers may view e-mail as more

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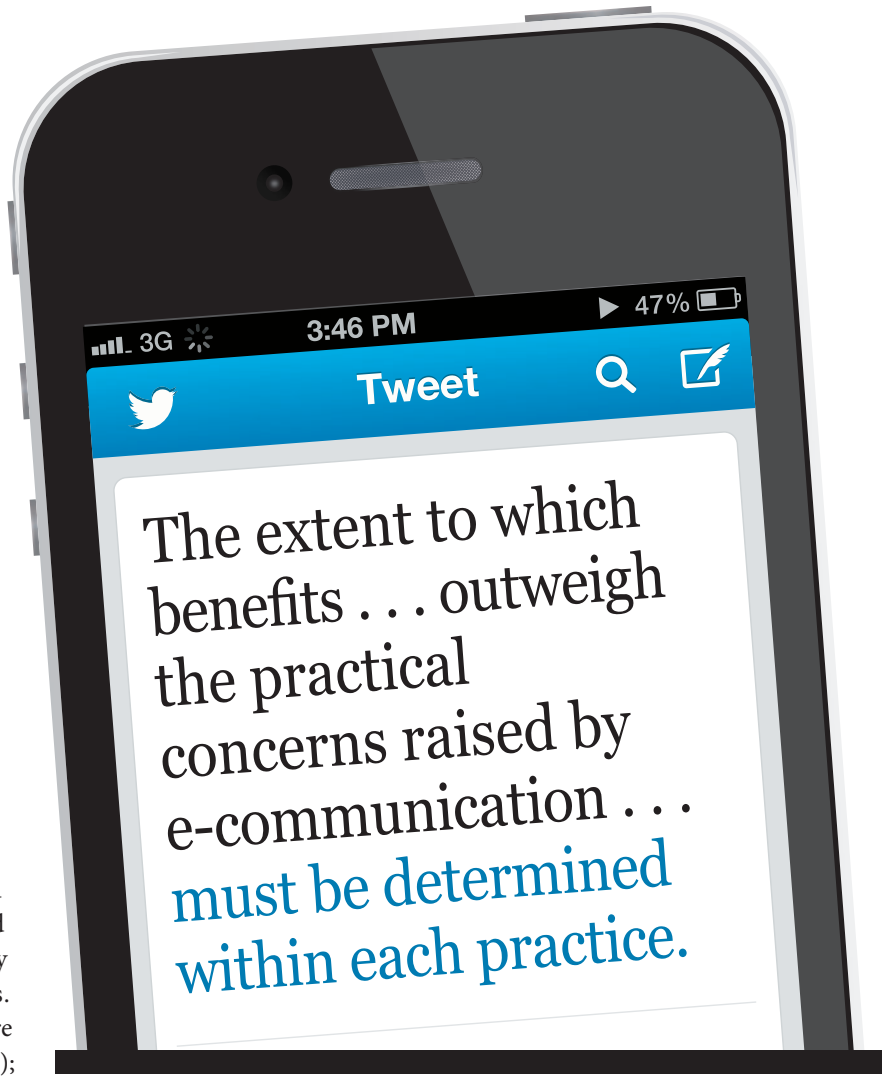
convenient than traditional "snail" mail, while not encroaching on an e-communication platform reserved for friends.

Mobile phones and texting—More than 75% of US adolescents own a cell phone, and teenagers are also the fastest-growing segment of smartphone owners in America.[2,3] In a 2011 survey, 75% of US adolescents said they text regularly.[1] Indeed, among teenagers who are online, their use of text messaging far surpasses the frequency of other forms of daily communication with their friends (Figure 1).[1]

Social media—A rapidly growing number of teenagers use social media, with more than half of adolescents reporting at least daily use.[4] Social media are defined as Web-based applications that allow the exchange of user-generated information in a virtual community.[4,5] They are often used to interact with specific groups with shared interests, ranging from groups of family members or friends to celebrity fan groups. Common platforms include Facebook (more than 14 million users aged 13 to 17 years[6]); Instagram, a popular photo-sharing program; and Twitter, a microblogging service for sharing brief messages publicly. Although the purpose of social media is sharing information, there are ways to limit access to posted content. For example, Facebook allows "secret" groups, such that membership is by invitation and only group members can see posts or the identity of other members. Although adolescents rate social media as an important means of communication, they also report that interactions via social media are not uniformly positive and some express that, at times, they wish they could return to a time before Facebook (36%).[5,7]

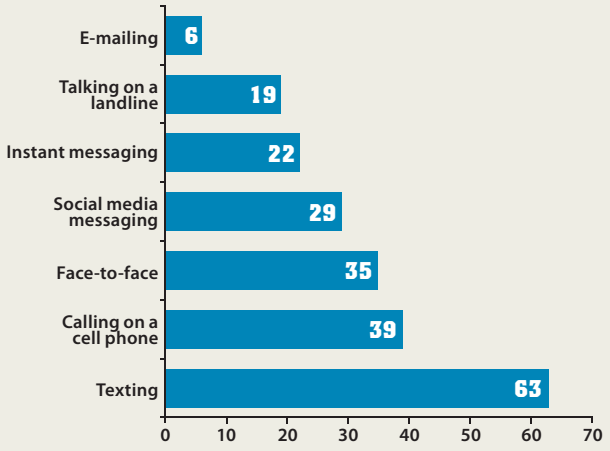
Video chatting—Adolescents have grown up with video chatting as a common feature available on the Internet, first with Skype, then FaceTime, and now with newer options such as ooVoo and Google Chat. Many adolescents are comfortable replacing in-person interactions with video interactions; this likely extends to interactions with health care providers.



Effectiveness of e-communication research interventions with adolescents

It is important to recognize that e-communication is not an inherent improvement upon current forms of communication. Of the few studies evaluating the impact of e-communication in health care interventions with adolescents, most have focused on text messaging, with mixed results. The studies showing positive outcomes generally targeted short-term behavior change or reminders. For example, an intervention notifying adolescents of test results by text messaging rather than standard methods improved the time to treatment for sexually transmitted infections (STIs).[8] However, for interventions targeting behavioral change over time, e-communication has been less effective. For example, a study using pedometers plus text messaging did not increase physical activity among adolescents with type 1 diabetes.[9] However, recent systematic reviews of studies using technology-based interventions

FIGURE 1 Means of communication used by adolescents daily (percent of online adolescents)



Adapted from Lenhart A.[1]

performed in a range of age groups have revealed benefits in smoking cessation, increases in patient adherence to HIV antiretroviral therapy, and modest improvements in clinic attendance with electronic appointment reminders. Although these studies were mainly in adults, and the reviews underscore the need for more rigorous research, they suggest the potential for e-communication to enhance care if implemented thoughtfully into pediatric practices with adolescents.[10,11]

Assessing the potential for e-communication in clinical practice

Selecting the appropriate form of e-communication with adolescent patients and establishing the parameters of use require consideration of a number of factors, some of which are addressed below.

Will e-communication be for business practice or clinical care?

Some routine *business operations* of a practice can potentially be accomplished via e-communication. For example, many practices send appointment reminders by mail or telephone; a switch to electronic reminders via e-mail or text message may be relatively simple because some billing and scheduling systems already support e-communication. This type of communication can be drafted without disclosing sensitive information, thereby minimizing patient privacy and security concerns. Providers should, however, be aware that acceptance of electronic reminders may be influenced by the frequency of the event for which reminders are sent and whether the recipients are parents or adolescents. Research exploring the use of reminders with parents has demonstrated moderate success with reminders about events such as annual influenza vaccines.[12] However, although a study involving daily blood sugar test reminders for adolescents with type 1 diabetes showed some positive results such as improved adherence, it did not significantly improve glycemic control and some adolescents complained about receiving the same message repeatedly.[13]

Electronic communications about *clinical care*, such as test results, present a greater concern. An entity that is covered by the Health Insurance Portability and Accountability Act (HIPAA) and that transmits protected health information (PHI) via e-communication is required to follow HIPAA's Security Rule, which mandates the implementation of safeguards to ensure that the patient's health information does not fall into the wrong hands. A 2013 study on text messaging of PHI demonstrated that every step of transmission poses unique risks that are not easily corrected.[14] For example, encryption—the gold standard for safeguarding e-mail—is not currently feasible for text messages. This raises the question of appropriate alternative safeguards for which regulators have not yet provided guidance. The decision of whether to implement e-communication for clinical care purposes thus ultimately rests on a number of risk-management considerations specific to the practice.

Although all PHI is protected under HIPAA, privacy and security concerns are especially high when sensitive information is involved, such as STI test results. In a survey of young adults aged 18 to 29 years, the respondents indicated that text messaging was not a preferred approach for receiving results of chlamydia testing.[15] In addition to the patient's possible discomfort with this approach, providers may have concerns about releasing potentially distressing information directly to adolescents, without the provider or a parent present to address questions or provide support.

Consequently, using e-communication for clinical care is less common than for business operations such as reminders, and implementing e-communication for clinical care requires greater effort and careful consideration. A potential option is using e-communication to notify adolescents to contact the practice to receive test results, without actually including any sensitive data. Alternatively, many health systems have incorporated patient portals (eg, MyUofMHealth.org) that allow users access to their health records via a protected Web site. These portals may also provide secure e-mail-like communication channels between the patient and provider. In these systems, an e-communication would need only to instruct the adolescent to check the patient portal for updated information.

Another use of e-communication in clinical care is to support *behavior change efforts* in the management of chronic conditions. For example, text messages have been used as a component of comprehensive adolescent weight-management interventions.[16,17] This is one of the few areas where there is growing experience with communicating directly with adolescents using electronic means, and research to date indicates that e-communication is welcome.[16] The acceptance of these initiatives may be due to the chronic nature of the patients' conditions and the embedding of e-communication within long-term clinical relationships with their providers.

Will the communication be initiated by the adolescent or the provider?

Adolescent-initiated e-communication may allow patients to describe their symptoms or health concerns, ask questions, or request prescription refills between clinic visits. This sort of contact increases convenience for patients but poses unique challenges. For example, implementation may require a mechanism for checking and responding to e-communications on an ongoing basis to ensure that urgent situations are addressed quickly. In addition, adolescents are relatively inexperienced at recognizing and describing symptoms, so providers may feel that the information received via text or e-mail is inadequate. To address these concerns, providers might limit adolescent-initiated e-communications to certain agreed-upon situations, such as planned reporting of specific symptoms, to allow monitoring over time.

Limiting e-communication to messages that originate from the provider or the practice allows greater control of both the timing and the content of the messages. The downside is that provider-initiated messages may be less engaging for adolescents, who may delete or disregard the messages when they are busy with school, activities, or social interactions.

Will the communication occur with teenagers individually or in a social media group setting?

Numerous patient-initiated and patient-directed social media groups have emerged for adults with a variety of conditions, ranging from cancer to mental health problems.[18,19] These groups allow patients to share information in a supportive environment. These groups could serve as a model for ways in which providers could communicate with adolescents who share specific diagnoses, to provide common information, and to foster communication among patients. However, providers should consider the risks associated with such groups and the need for close monitoring. For example, if an adolescent were to post a disconcerting symptom on a clinic Facebook page and later have a poor outcome, the provider could face liability if the posts were not monitored and timely follow-up was warranted but not provided.

Beyond these concerns, it is unknown whether parents would support their adolescents' participation in such groups. Furthermore, teenagers may prefer to reserve certain communication channels for their friends and not wish to interact via social media with health care providers or patient peers. Finally, social media present unique privacy concerns. Facebook is well known for constantly changing its privacy policy and altering default privacy settings without advance warning. Therefore, providers and patients should be aware that privacy breaches may occur.

How are e-communications perceived?

Physicians/Providers—Although little is known about physicians' preferences related to e-communication with adolescents, a 2012 study exploring perspectives of clinical and administrative staff at primary care practices regarding e-mail and text-message communications with parents is

instructive.[20] The study revealed several areas of concern, including cost to the practice, parental preferences, patients' privacy, legal requirements, and potential liability for unanswered messages. These concerns are likely to be amplified when considering e-communication with adolescent patients.

One of the few studies focusing on e-communication with adolescents in primary care explored providers' perceptions of texting teenagers. The study revealed more support for lower-risk and lower-cost uses such as appointment and medication reminders (86% and 77%, respectively) than for potentially riskier uses such as receiving adolescents' updates about their health (63%) and providing test results (55%).[21] The providers indicated that health care-related text messaging was appropriate at a mean age of 14.6 years, and some of the above concerns may decrease when communicating with older adolescents. Other issues, such as reimbursement for e-communication and legal concerns, may diminish as new technologies become a routine part of care.

Parents—Knowledge of parents' perspectives about e-communication from providers directly to adolescents is also limited. One study showed that although parents widely accepted provider-to-adolescent text messaging, approval was higher when parents were privy to the content of the adolescents' messages to their providers. Parental acceptance was also influenced by the age of the adolescent and the purpose of the communication; acceptance was higher for business purposes such as reminders, and acceptance was lower for clinical care purposes such as monitoring adolescents' health conditions (eg, pain status).[21]

Adolescents—Judging from the existing literature of small-scale studies, adolescents' views about e-communication are nuanced and situation dependent. One study found that although parents and providers were amenable to text messaging immunization reminders to adolescents, the adolescents themselves associated text messaging with friends and thought it was "weird" for their primary care providers to text message them.[12] In another study, most adolescents expressed positive views about receiving STI prevention information via text message, although a few indicated concern that others might see the content of their messages.[22] In regard to behavior-change efforts, adolescents participating in weight-management programs have welcomed text messages from program providers.[23] This may suggest that texting is acceptable when adolescents invite the communication about a specific topic, but that they are less likely to embrace communications that are physician initiated or that address sensitive issues or topics about which they have not specifically expressed interest.

Practical advice for providers

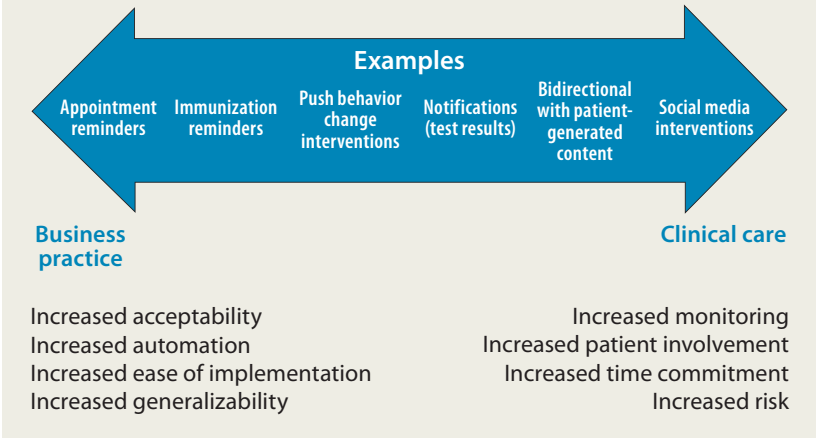
The purpose of the e-communication, the extent to which it matches the resources of the practice, and the costs associated with its use should influence the decision of whether and how to use e-communication with adolescents. When e-communication is used for operational purposes such as appointment reminders, the most salient issues may be collecting, storing, and updating adolescents' e-mail addresses and mobile phone numbers within the practice management system or electronic medical record (EMR). For communications involving clinical care, the issues will be more complex. The following actions should be taken before initiating e-communication with adolescents.

Obtain legal and/or risk-management advice early—Any provider contemplating introducing e-communication into his or her practice should consult an attorney and/or risk-management consultant early in the planning stages to identify possible risks. Potential problems can range from the relatively simple, such as ensuring that information sent via e-communication is also entered into the EMR, to the more complex, such as HIPAA compliance. Providers interested in transmitting PHI should be aware that this area of law is nuanced, and although there is guidance on how these laws apply to technology such as e-mail, it is often unclear how best to safeguard newer technologies such as text messaging.

Assess parents' and patients' preferences—Views about e-communication vary broadly, so providers should ascertain the preferences of patients and parents. This may involve administering a practice-wide survey to determine a single "best fit" for the practice, or developing a mechanism to customize e-communications to match preferences at

an individual level. Parents should be asked whether they are comfortable with providers' communicating directly with their adolescents, whether they wish to be copied on the communication (if they are entitled to be included), what information they feel comfortable having addressed in this way, and what parameters they would like in place (eg, time of day and frequency of messages). In addition, adolescents' communication preferences should be assessed, including whether they want messages sent to them at all; whether they prefer text, e-mail, or social media communication; and what types of messages and topics they are willing to receive.

FIGURE 2 The electronic/mobile communication continuum



Develop a thorough consent process—The foundation of consent should be an overview of what to expect, a discussion of the inherent limitations of communicating electronically, and, if relevant, an opportunity to opt out. Because parents often must provide consent for an adolescent's health care, parents should also consent to their adolescents' receiving e-communications. Adolescents should also provide their consent. For certain confidential health services that adolescents can consent to on their own under state law, no parental consent is required for them to receive e-communications (eg, STI testing and treatment). However, providers should ask adolescents receiving those confidential services how they would like to be contacted. Adolescents may not prefer e-communications if, for example, their parents have access to their cell phones. The consent process is also an ideal time to discuss the importance of using e-communication technologies safely; for instance, not texting while driving.

Determine practice parameters—A clear policy outlining the parameters for e-communication (eg, age at which providers may contact adolescents directly, time of day that communications will be sent, and frequency of communications) will help avoid problems with implementation and liability. Of particular importance is gaining consensus within the practice on what types of information will be conveyed, when parents should be notified, and whether patient-initiated communication will be allowed.

Implement a monitoring protocol—The broader the parameters of e-communication, the greater the need for monitoring. For example, social media used for clinical care purposes should be monitored for any unsuitable or inaccurate content posted by adolescents or any information about their health status that requires action. Terms of use should be clearly communicated, along with the course of action that will be taken should specific concerns arise, and a plan must be implemented to identify potential problems. This plan should address how coverage will be provided in off-hours (ie, evenings, weekends, and holidays) and what to do in case of emergencies.

Summary

E-communication can be considered on a continuum ranging from uses focused on practice operations to those that are a more integral component of clinical care (Figure 2). Uses on the operational end of the spectrum require limited personnel oversight, are easily automated and scaled to include a large number of patients, and may be generalized to a variety of practice settings and for a range of issues (eg, immunization, screening tests, and appointment reminders). These are typically provider-initiated messages sent without allowing free text responses from patients (although they may permit brief confirmation responses to indicate receipt and intent to keep the appointment). These

uses may be more widely considered appropriate for direct contact with adolescents because the messages are less likely to include sensitive information and the message content is under provider control. However, more investigation is required to learn adolescents' general preferences about receiving such messages.

Moving across the continuum are e-communications integrated into clinical care. These communications may extend the flow of information between providers and patients beyond in-person clinic visits. Parents and adolescents may have varying perceptions of providers' communicating directly with teenagers depending on the type of information being communicated, and this warrants a consent procedure to ensure that families are well informed. This type of contact with adolescents allows richer communication but requires more personnel time and presents greater risk.

The spectrum of e-communication options offers a number of potential benefits for patients and providers, including remote symptom monitoring, enhanced adherence via reminders, promotion of behavior change, and a decrease in clinic visits. Beyond primary care, e-communication may be helpful in other settings where adolescents are seen, such as emergency departments that might check on discharged patients. However, the extent to which benefits are realized and the degree to which they outweigh the practical concerns raised by e-communication depend upon the specifics of implementation and must be determined within each practice.

ACKNOWLEDGMENTS

The authors are grateful for the assistance provided by Emily Klatt, JD, for input regarding the legal considerations of e-communication with adolescents, and by Sally Askar for her help in preparing the background for this paper.

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Are obese kids more vulnerable to food advertising than their healthy-weight peers?

A recent investigation found that compared with healthy-weight children, those who are obese show significantly less brain activation in regions associated with cognitive control after viewing familiar food logos, such as McDonald's "golden arches." This suggests that obese children may be more responsive to food advertising than their normal-weight peers.

To select the most appropriate food and nonfood logos for their study, investigators asked 32 children to rate on a 5-point scale 239 brand logos as to familiarity, valence (happy/sad), and arousal (exciting/boring). Based on the children's ratings, investigators chose 120 highly familiar logos: 60 food logos and 60 nonfood logos, such as the Nike "swoosh."

Twenty other children aged from 10 to 14 years were recruited from pediatric clinics for the study itself. Half the children had a mean body mass index (BMI) in the 50th percentile and the other half a BMI in the 98.9th percentile. After being weighed and measured and having their self-control assessed with a self-report measure, the study subjects underwent functional magnetic resonance imaging while viewing the food and nonfood logos. When viewing food logos, the healthy-weight children showed greater brain activation than the obese children in regions associated with cognitive control and self-control. Specifically, the healthy-weight children showed greater activation bilaterally in the Brodmann area 10 and the inferior frontal gyrus (Bruce AS, et al. *J Pediatr.* 2013;162[4]:759-764.e2).

COMMENTARY

So, some of us are hardwired to be more susceptible to marketing and other external stimuli to eat. If this trait is genetically coded, and it seems that nearly everything is, it may explain some familial obesity and the difficulty of changing family eating habits.

—Michael Burke, MD

ADHD POSES SIGNIFICANT LONG-TERM HEALTH RISKS

Having attention-deficit/hyperactivity disorder (ADHD) in childhood increases the risk for suicide in adulthood and for having 1 or more psychiatric disorders other than ADHD, a large prospective epidemiologic study shows. The study also found that ADHD persists into adulthood in nearly one-third of children with childhood ADHD.

Investigators studied a large birth cohort of children born in Rochester, Minnesota, between 1976 and 1982. From this group, they collected prospective data for 232 adults (mean age, 27 years) with childhood ADHD and 335 controls (mean age, 28.6 years) without childhood ADHD, administering standardized neuropsychiatric interviews to study participants. In addition, they compared overall and cause-specific mortality in those with childhood ADHD and the remainder of the entire birth cohort (4,946 individuals) without the condition.

ADHD persisted into adulthood in 29.3% of those with childhood ADHD who were in the prospective study. Participants with childhood ADHD were more likely than controls—56.9% vs 34.9%—to have 1 or more comorbid psychiatric disorders, most often alcohol dependence/abuse (26.3%) followed by other substance dependence/abuse, current or past history of a hypomanic episode, generalized anxiety disorder, or current major depressive episode. Compared

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with participants who had childhood ADHD that did not persist, those with persistent ADHD were much more likely to have 1 or more comorbid psychiatric disorders (80.9% vs 47.0%, respectively).

Individuals with childhood ADHD were also at greater risk than others in their birth cohort of death—not significantly overall or by accident, but specifically by suicide. Of 7 individuals in the original birth cohort identified as having childhood ADHD who had died, 3 were suicides; 5 had a previous history of both substance use disorder and 1 or more other psychiatric comorbidities (Barbaresi WJ, et al. *Pediatrics*. 2013;131[4]:637-644).

COMMENTARY

What happens to our patients with ADHD when they grow up? For the 30% of patients who carry the diagnosis of ADHD into adulthood, is there a transition of care to a medical provider for adults who is comfortable treating ADHD? Data reported here don't include information on whether or not the adult patients studied were treated for ADHD in adulthood. If their condition were treated, would their rate of suicide and likelihood of other psychiatric disorders be changed? This study may generate the questions for which answers will bring adult ADHD into better focus.

—Michael Burke, MD

CHILDHOOD MIGRAINE MAY BE ASSOCIATED WITH INFANT COLIC

Children with migraine—with or without aura—are significantly more likely to have had colic as infants than children without migraine, according to a case control study conducted in France and Italy.

Investigators identified 208 patients aged from 6 to 18 years who received a diagnosis of migraine by a pediatric neurologist after visiting an emergency department (ED). The 471 control participants were children in the same age range who visited the ED of the 3 participating centers for minor trauma. Parents of study participants completed a structured questionnaire to determine the patient and family history of infantile colic, which investigators confirmed by reviewing the children's personal medical records.

In children with migraine, 72.6% reported infantile colic compared with 26.5% of children in the control group. In the migraine with aura group, the prevalence of colic was 69.7% and in the migraine without aura group it was 73.9%. The association between headache and infantile colic was not found for children with tension-type headaches, examined in a separate study in 120 children, confirming the specificity of the association between migraine and colic (Romanello S, et al. *JAMA*. 2013;309[15]:1607-1612).

COMMENTARY

This is an eye-opening study with some interesting implications. Maybe all our attention to the bellies of babies with colic has been misdirected. Or perhaps the same pathology (or genetics) that causes migraine headaches in adults causes abdominal pain in infants and cyclic vomiting and abdominal migraines in children. Maybe someday we'll be using probiotics to prevent migraines and beta-blockers to prevent colic. I am looking forward to seeing where this observation leads.

—Michael Burke, MD

Also of Note

A new study suggests measuring zinc protoporphyrin (ZPP) to screen for iron deficiency. Analysis of baseline screening results for complete blood cell count, lead, and ZPP based on blood draws from more than 2,600 children aged between 8 and 18 months and during follow-up found that almost half had abnormally high ZPP levels. Among those with anemia and abnormal ZPP at baseline, 81.5% of those prescribed iron showed a reduction of ZPP at follow-up compared with 69.7% of those not prescribed iron (Magge H, et al. *JAMA Pediatr*. 2013;167[4]:361-367).

GENETIC TESTING FOR INTELLECTUAL DISABILITY

A ROLE IN DIAGNOSTIC EVALUATION

CHRISTA W HABELA, MD, PHD, AND ADA HAMOSH, MD, MPH

Recent AAP guidelines on genetic testing in children warrant pediatricians' awareness of the newest screening modalities.

Intellectual disability (ID) is a condition with a prevalence of 1% to 3%.[1-5] As a result, most pediatricians will be required to address and manage this condition on a regular basis. In many circumstances an underlying etiology has been identified, but often the diagnosis of ID or global developmental delay (GDD) is made by a pediatrician and there is no immediately apparent underlying explanation. Establishing an underlying diagnosis has numerous implications beyond just medical treatment and should be considered a priority of patient care.

There are numerous causes of ID, but prenatal causes are by far the most common. Of these, genetic abnormalities predominate. If a diagnosis is not made after conducting an appropriate history and physical examination, genetic testing, and specifically a chromosomal microarray, is considered the first-line procedure in the diagnostic evaluation of ID, according to the American Academy of Neurology, the Child Neurology Society, and the American College of Medical Genetics.[1,4,6] This article reviews the role of chromosomal microarray in the diagnosis of ID/GDD.

Definition of ID/GDD and importance of a diagnosis

Intellectual disability is defined as consistently subaverage intellectual function that is accompanied by defects in adaptive, conceptual, or social skills with onset before 18 years of age.[3] The diagnosis and subclassification into mild, moderate, and severe ID are made based on IQ testing; an IQ of less than 70 is the minimum criterion for mild ID. GDD is defined as performance that is 2 standard deviations below age-appropriate norms in 2 or more areas of development and is a more useful definition in children who are aged younger than 6 years for whom IQ testing cannot be performed.[1] GDD is often a precursor to ID, and pediatricians are obligated to conduct a diagnostic evaluation before a child is capable of completing IQ testing. Therefore, ID and GDD are used interchangeably here.

Establishing a diagnosis of ID can be labor intensive and may require the involvement of subspecialists. However, regardless of the availability of specific treatment or cure, knowing the diagnosis may have far-reaching benefits for the patient and family and justifies

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TABLE Key components of history and physical examination in the evaluation of intellectual disability

Category	Specific evaluation	Rationale
History	Prenatal and birth history	Most cases of intellectual disability stem from events surrounding birth.
	Developmental history	Details of developmental milestones and time course of progression or regression will give clues as to a static or ongoing process.
	Family history with 3-generation pedigree	A 3-generation pedigree is critical in identifying familial syndromes.
Physical examination	Screening for other affected organ systems	Comprehensive exam may reveal other affected organ systems, giving a clue to the diagnosis.
	Morphologic abnormalities	Morphologic and behavioral abnormalities are critical in syndromic diagnoses.
	Behavioral abnormalities	See above.
	Detailed neurologic exam	A detailed neurologic exam may reveal additional neurologic deficits.

From Moeschler JB.[9]

the effort. Identifying an underlying genetic cause may give a better indication of prognosis as well as recurrence risk for the patient and family. Along those same lines, a genetic diagnosis may provide the ability to anticipate associated comorbidities and other affected organ systems that have not yet been recognized. From a practical standpoint, a diagnosis will also help families gain access to services. These services may range from disease-specific therapies to financial assistance and support groups, all of which are likely to improve quality of life for both the patient and family and should not be undervalued.

Numerous causes of ID have been identified. These include, but are not limited to, genetic abnormalities, infection, trauma, complications of extreme prematurity, toxic exposures, hypoxia, hemorrhage, malnutrition, or metabolic and endocrine abnormalities. Of the metabolic, toxic, and infectious etiologies, prenatal and neonatal injuries are the most common. A child with ID may have one of these causes readily identifiable. However, up to 60% to 80% of children will not have a readily identifiable underlying diagnosis.[7,8] A genetic evaluation is therefore indicated as part of the diagnostic evaluation of these children. Ideally, a consultant with genetics training would guide this process. However, time constraints may make this difficult, and geographic proximity would be necessary. An understanding of the utility of current diagnostic techniques may enable the pediatrician to expedite this process.

Clinical evaluation of ID/GDD

As with all pediatric illnesses and conditions, a detailed history and physical examination are paramount when evaluating the underlying etiology of ID (Table).[9] Various studies have suggested that the history and physical examination alone are responsible for a diagnosis in one-third to two-thirds of cases of ID. The history should focus on prenatal and birth history, developmental history, and family history. Additionally, given the prevalence of genetic disorders in ID, a 3-generation pedigree should be obtained when possible. The physical examination should be comprehensive, with a high suspicion for other affected organ systems that may give a clue to the diagnosis. A detailed neurologic examination should be conducted to look for other signs of diffuse or focal abnormalities that may indicate a need for neuroimaging. These signs include abnormalities in strength, tone, and coordination, especially when any findings are asymmetrical. Finally, attention should be paid to any morphologic or behavioral abnormalities that may aid in narrowing the differential diagnosis given their association with specific syndromes. Some examples include macrocephaly or

microcephaly; abnormal positioning of the eyes and ears; overdeveloped or underdeveloped sexual characteristics; and behaviors such as tics, abnormal movements, aggression, or inappropriate affection.

Upon completion of the history and physical examination, there are multiple possible results that will determine the type and extent of further testing. A diagnosis may be made based on history and physical examination alone (eg, the history reveals significant intrauterine alcohol exposure and the patient has morphology and behavior consistent with fetal alcohol syndrome). In this case, further testing may not be warranted. However, more commonly, the history and physical examination suggest etiologies that require further testing. A suspected metabolic or endocrine abnormality requires diagnostic or screening laboratory testing (eg, thyroid function studies for hypothyroidism or screening fasting plasma amino acids and urine organic acids for suspected inborn errors of metabolism). Similarly, a specific genetic syndrome may be suspected but requires confirmation (eg, specific testing for Rett syndrome in girls with developmental regression and microcephaly, or G-banded karyotype for infants with examination findings consistent with trisomy 21). Finally, patients may have isolated ID with or without focal neurologic findings but with no hints as to an underlying etiology. In these 2 groups of patients, genetic testing is critical. Chromosomal microarray along with fragile-X testing is currently considered the most sensitive and comprehensive test when a specific diagnosis is not suspected.[1,4,6]

Genetic testing for ID/GDD

Karyotyping was first used to identify trisomy 21 in 1959. Since that time, genetic testing has evolved tremendously, and the question of what modality is most clinically useful and cost-effective has become more pertinent. During the past 5 years, multiple studies have clearly demonstrated that chromosomal arrays are the highest-yielding diagnostic tools for ID of unknown etiology and are preferred over G-banded karyotypes (standard karyotyping) and fluorescence in situ hybridization (FISH) assays. The exception would be cases of clinically recognizable aneuploidy syndromes or a family history of balanced translocations or multiple spontaneous abortions.[1,4,10-15]

Chromosome microarrays are assays that use fluorescence-based technology to detect copy-number changes (duplications and deletions) across the genome. There are 2 commonly used types of arrays.[6,10] The first is comparative genomic hybridization (CGH; Figure 1A). This technique compares the amount of fluorescently labeled DNA from a patient sample that is bound to known DNA sequences to the amount of DNA from a healthy control sample that binds to the same DNA sequences. This type is usually called an oligoarray and spans the length of all chromosomes, with enrichment in known areas of copy-number variation. Most oligoarrays have 144,000 to 180,000 probes. The second type of array is a single-nucleotide polymorphism (SNP) genotyping array (Figure 1B). SNP arrays take advantage of multiple sites in the genome where 2 different alleles are present in the general population. The 2 different alleles are differentially fluorescently labeled and hybridized with patient DNA. The total fluorescence and the fluorescence ratio of the 2 different dyes allow analysis of homozygosity and heterozygosity as well as identification of duplications or deletions. Most SNP arrays detect 660,000 to 2 million SNPs across the length of all chromosomes.

It should be noted that SNP arrays are capable of detecting consanguinity and uniparental disomy, whereas CGH arrays are not.[3,10,16] Studies looking at the diagnostic yield of CGH and SNP arrays have reported a yield of 10% to 30%, with the majority of studies reporting 15% to 20%.[1,4,10-15] In contrast, G-banded karyotyping detects abnormalities in only 2% to 4% of cases, and FISH in 2.4% to 3.5%.[1,4]

It has been argued that the use of microarrays will cause an inability to detect balanced translocations. Balanced translocations result from an exchange of material between nonhomologous chromosomes resulting in the same absolute amount of DNA that is located on a different chromosome. This creates the potential for interruption of coding or regulatory sequences. Because a microarray detects only copy-number variation (how many copies of a sequence are present) and not organization (where the sequence is present), there is a theoretical risk of missing a balanced translocation. However, many balanced translocations at the resolution of the G-banded karyotype are not balanced at the molecular level, and there is a

CONTINUED ON **PAGE 27**

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.*

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

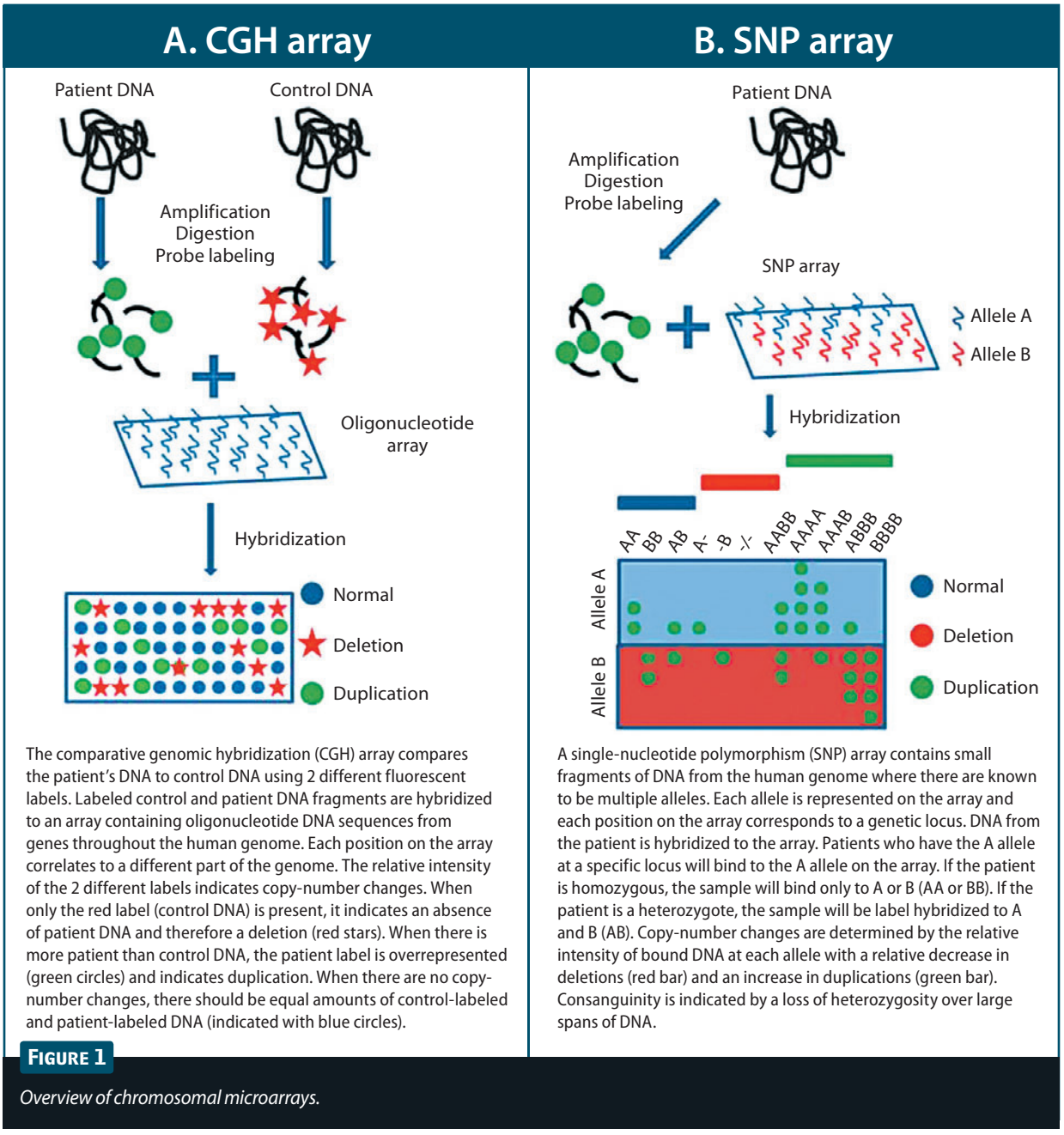
CONTINUED FROM **PAGE 23**

copy-number change that can be detected by microarray. Additionally, balanced rearrangements account for only a tiny minority of changes in patients with ID, and the routine use of G-banded karyotyping is not indicated to capture these events. Further, chromosomal microarrays have a similar ability to detect mosaicism as G-banded karyotyping. Generally, 20 cells are analyzed in a routine karyotype, and a minimum of 3 abnormal cells is indicated before 50 cells are analyzed. Thus, the lower limit for detection of mosaicism is 14%, and most laboratories quote 20%. The CGH array is comparably sensitive. The SNP arrays can detect mosaicism at a resolution of 5%.[4]

Although the chromosomal array should be the standard testing modality in most cases, there are limited indications for the use of G-banded karyotype in addition to or instead of an array. These scenarios include clinically recognizable aneuploidy syndromes such as trisomy 21, 18, or 13, or Turner (45,X) or Klinefelter (47,XXY) syndromes; more than 2 spontaneous abortions; or a known family history of balanced translocations.[4] In the latter 2 cases, there is likely to be a parental chromosomal abnormality present. Therefore, karyotyping of the parents would also be recommended for further characterization and genetic counseling.

Although trisomy 21 is the most common chromosomal abnormality associated with ID, fragile X syndrome is the most common single-gene defect linked to ID and accounts for 1% of all males and about 0.3% of females with ID. Although postpubertal males develop a long face and macroorchidism, younger boys and affected girls have no specific phenotype. Therefore, fragile-X testing should be performed in addition to a microarray in the initial evaluation of nonsyndromic ID.[9]

Some specific syndromes are easier to identify clinically, and specific testing for these syndromes is warranted in addition to a microarray. These syndromes include X-linked forms of ID (XLID) in boys and Rett syndrome in girls. In boys, XLID is believed to account for 10% of ID, and approximately 90 XLID genes have been identified to date.[7] A family history suggestive



The comparative genomic hybridization (CGH) array compares the patient's DNA to control DNA using 2 different fluorescent labels. Labeled control and patient DNA fragments are hybridized to an array containing oligonucleotide DNA sequences from genes throughout the human genome. Each position on the array correlates to a different part of the genome. The relative intensity of the 2 different labels indicates copy-number changes. When only the red label (control DNA) is present, it indicates an absence of patient DNA and therefore a deletion (red stars). When there is more patient than control DNA, the patient label is overrepresented (green circles) and indicates duplication. When there are no copy-number changes, there should be equal amounts of control-labeled and patient-labeled DNA (indicated with blue circles).

A single-nucleotide polymorphism (SNP) array contains small fragments of DNA from the human genome where there are known to be multiple alleles. Each allele is represented on the array and each position on the array corresponds to a genetic locus. DNA from the patient is hybridized to the array. Patients who have the A allele at a specific locus will bind to the A allele on the array. If the patient is homozygous, the sample will bind only to A or B (AA or BB). If the patient is a heterozygote, the sample will be label hybridized to A and B (AB). Copy-number changes are determined by the relative intensity of bound DNA at each allele with a relative decrease in deletions (red bar) and an increase in duplications (green bar). Consanguinity is indicated by a loss of heterozygosity over large spans of DNA.

FIGURE 1

Overview of chromosomal microarrays.

of X-linked inheritance is highly predictive of a mutation and indicates the need for specific testing. In girls, *MECP2* gene studies are positive in approximately 1.5% of screened individuals with clinical criteria suggestive for Rett syndrome,[1] including acquired microcephaly, loss of purposeful hand movements with concomitant development of hand wringing, and loss of verbal and gross motor skills, following a period of at least 6 months of normal development. In each of these cases, specific testing would be an adjunct to (not a replacement for) chromosomal microarray.

Expert consultation and family counseling

The pediatrician will be the first to identify ID/GDD without an identified cause after the history and

physical examination. At this point, samples for fragile-X testing and chromosomal microarray may be sent after appropriate pretest counseling. Although most geneticists would welcome consultation at any point in this evaluation, and a pediatrician may choose to defer this process to a genetics consultant, the family may have physical or financial barriers to accessing consultants. Regardless of the clinician who initiates genetic testing, taking this first step provides a significant likelihood of finding a diagnosis. If the results of the array are inconclusive or require further testing and therefore genetics consultation, the family is at least 1 step further along in the process.

Whether a chromosomal array is ordered by the pediatrician or a consultant, the family should be appropriately counseled by the person sending the test. At a minimum, the pediatrician should make the family aware of the possible outcomes of testing. The first possibility is that a diagnosis will be made. If this is the case, management may or may not change, but a diagnosis may predict other organ-system involvement that has not yet manifested, and it may have implications for access to services as well as for health issues in other family members. A second possibility is that a copy-number variation is identified, but it has unknown significance and causality cannot be established. This may require additional testing of the patient and the parents as well as other family members and will require the involvement of specialists. The third possibility is that no abnormality is detected. Other avenues may be pursued, or the patient will have to be reevaluated after a period of time. Finally, there is a chance that the family finds out something unrelated to ID that they do not want to know about, such as deletions or duplications involving a cancer or late-onset neurologic disease. In addition, the parents must be informed that consanguinity will be detected when SNP arrays are used. The significance of this counseling is emphasized by the American Academy of Pediatrics policy statement, "Ethical and Policy Issues in Genetic Testing and Screening of Children," published in February 2013.[17]

The importance of establishing a diagnosis cannot be overstated. It can stop the diagnostic odyssey and permits accurate counseling about prognosis and recurrence risk. If a diagnosis is not established after an initial evaluation, the patient should be retested every 6 to 12 months during the first 3 years of life and every 1 to 2 years thereafter. It is worthwhile to initiate a new genetic evaluation in an older patient who may have only been offered karyotyping early in life. This is especially important if reproductive capacity is a concern or if other siblings may be carriers. These patients and their family members are just as likely to benefit from a diagnosis, and there is a much higher probability of diagnosis with chromosomal microarrays.

Other diagnostic procedures

The current data suggest that chromosomal microarrays are a first-tier test in the evaluation of ID and, in addition to fragile-X testing, should be considered second only to an appropriate history, physical examination, and pedigree (Figure 2).[3] An additional early diagnostic tool is magnetic resonance imaging (MRI) of the brain. This is specifically warranted when there are focal or diffuse findings on neurologic examination or the presence of macrocephaly, microcephaly, or facial abnormalities suggestive of brain malformation. Additionally, a history of focal or intractable seizures, developmental regression, progressive neurologic deterioration, or movement abnormalities may suggest that an MRI will reveal abnormal structure.[3,9] However, it should be noted that abnormal MRI findings may only further characterize a process without necessarily providing an underlying etiology.[9]

Costs and insurance coverage

Both CGH and SNP arrays are commercially available and provide more sensitive analysis of the genome than a karyotype for a comparable price (the cost of a karyotype is $700 to $1,200; a SNP array costs $1,500 to $2,000). These tests are covered by private insurance companies, Medicaid, and Medicare, but they may require a letter of medical necessity, depending upon the insurer. Whole-exome analysis is the next advance in genetic testing and offers sequencing of about 90% of the protein-coding region of the genome for the same cost as sequencing just a few genes. It will likely increase the sensitivity of detecting genetic changes in ID in the future. This technology is rapidly evolving and the counseling required is quite complex, both before and after testing. Therefore, if microarray and

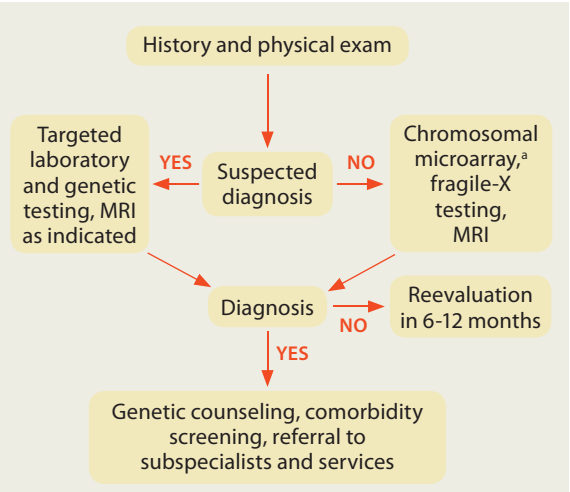


FIGURE 2

Overview of the diagnostic approach to intellectual disability of unknown etiology. A comprehensive family, prenatal, birth, and developmental history, including a 3-generation pedigree, and physical examination are of utmost importance. Referral to a specialist is indicated at any point in the evaluation and is strongly recommended if the initial evaluation is inconclusive or if a positive diagnosis requires genetic counseling. Magnetic resonance imaging (MRI) may be used as an adjunct to diagnosis and is specifically indicated early in the evaluation based on history (eg, seizures or developmental regression) and focal neurologic or craniofacial findings.
[a]Pretest counseling should be performed before sending samples for a microarray and should include the possible discovery of consanguinity when a single-nucleotide polymorphism (SNP) array is scheduled.
Abbreviation: MRI, magnetic resonance imaging.
Adapted from Mefford HC, et al.[3]

fragile-X testing are unrevealing, a genetics consultation is the next step for the patient with ID.

Summary

Intellectual disability is a prevalent condition that pediatricians should expect to encounter. Establishing a diagnosis is mandatory for optimal patient care, patient and family counseling about prognosis and recurrence risk, and access to health care services. Because of the predominance of genetic causes of ID, chromosomal microarray (CGH or SNP) is a critical second step after a detailed history and physical examination. With sufficient knowledge, pediatricians can begin the process of genetic diagnosis until specialist consultation becomes necessary. A case of ID/GDD of unknown etiology should be considered a diagnosis in progress and should be reevaluated as genetic testing continues to evolve. CP

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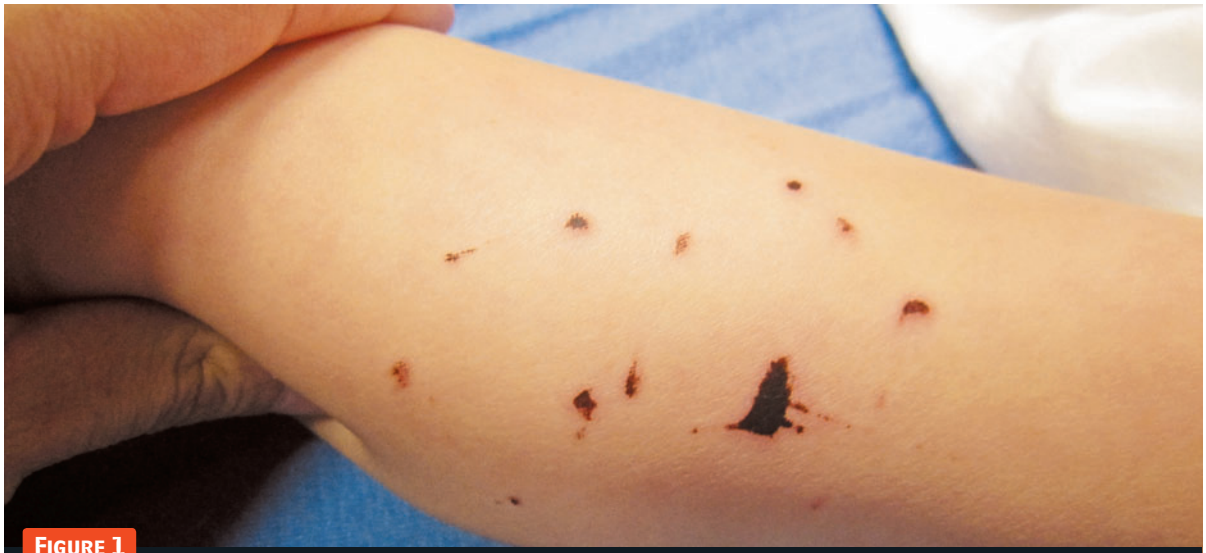

FIGURE 1
Black spots in geometric patterns on the lower leg of a 2-year-old boy.

Black spots on a toddler's skin

EUPHEMIA W MU, MS IV; BRIAN C CAPELL, MD, PHD; AND LESLIE CASTELO-SOCCIO, MD, PHD

THE CASE

You are called to the emergency room to evaluate a healthy 2-year-old boy with black spots on his legs that were noted yesterday evening. His younger brother developed similar black spots this morning. The boys are healthy, and the lesions are not symptomatic and appear to be superficial.

FOR DISCUSSION SEE PAGE 32

TELL US ON FACEBOOK

Have you ever had an experience in your practice with a case such as this? Share your story with us on Facebook.
facebook.com/ContemporaryPediatrics

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DIAGNOSIS:

Black spot poison ivy

CLINICAL FINDINGS AND ETIOLOGY

The dark black-brown macules and patches range from 1 mm to 1 cm in size with thin surrounding rims of erythema on the patient's arms and legs (Figure 1). Under dermatoscopic magnification the macules and papules follow normal skin markings in linear dark streaks, suggesting that they are superficial (Figure 2). A few dark areas can be reduced slightly in size using an alcohol pad, but most are persistent despite vigorous rubbing. Blood work and urinalysis are all within normal limits.

FIGURE 2

Dermatoscopic magnification of a black spot on the leg of a 2-year-old boy.

These skin findings are typical black spot poison ivy in a child who has no previous exposure to poison ivy or another member of the *Toxicodendron* genus. An estimated 85% of the North American population is sensitive to these plants, the most common of which are poison ivy (*Toxicodendron radicans*), poison sumac (*Toxicodendron vernix*), and poison oak (*Toxicodendron diversilobum or Toxicodendron pubescens*).[1]

The skin lesions resulting from the hypersensitivity reaction to this family of plants are usually erythematous, extremely pruritic, grouped or linear papules and/or vesicles appearing on exposed areas 24 to 48 hours after contact.

Black spot poison ivy is an uncommon presentation following exposure to urushiol or oleoresin, an irritant and allergen from the *Toxicodendron* genus.[2] This plant resin oxidizes and turns black when exposed to air.[3]

Black spot poison ivy is rare because it requires exposure to concentrated sap. In one study, patients exposed to undiluted concentrations of urushiol developed black spots, while those exposed to a 1 to 50 dilution experienced papulovesicular dermatitis but not black spots.[4]

Given the superficial nature of these lesions, lack of symptoms, and the clinician's suspicion of black spot poison ivy, a biopsy is deferred. Histopathology would have shown amorphous yellow material in the stratum corneum and epidermal areas of coagulation necrosis.[5]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of black macules and patches includes superficial purpura, marker or ink, tinea nigra, and black spot poison ivy. If the lesions appear necrotic, infectious and noninfectious vasculitis should be considered. It is important to distinguish the level of skin affected. The involvement of exposed areas and linear/geometric configuration of individual lesions suggest that the dark spots most likely originated from an outside source. A clinical history of exposure to poison ivy supports the diagnosis of black spot poison ivy. Interestingly, since these lesions usually occur with first exposure to poison ivy, a patient usually does not develop the typical itchy eczematous eruption characteristic of poison ivy.

OUR PATIENT

The treatment of black spot poison ivy is similar to that of allergic contact dermatitis from poison ivy.[6]

Once the oleoresin is oxidized and bound to skin, the black spots cannot be removed with soap, water, or alcohol. The black spots gradually desquamate 1 to 2 weeks after formation without scarring. Patients should also clean or throw out clothing and evaluate for possible sources of poison ivy exposure.

In this case, the parents found poison ivy in the yard and developed blistering lesions of their own skin 2 days later.

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Improving patient care:
Smartphones and mobile medical devices

Mobile medical gadgetry is in its infancy, yet these devices can help you motivate pediatric patients and their parents to adopt healthier lifestyles.

The world is a much different place since the iPhone was released this month just 6 years ago in 2007. Because of our smart mobile devices, we talk, text and tweet, shop wisely, travel expediently, and socialize even when alone. Our smartphones and tablets challenge us with games, amuse us with music and books, and entertain us with television shows and movies. As they have become everyone's constant companion, patients and parents waiting for medical visits use their mobile devices to play games or read e-mail, play music, text a friend, or watch a video. No one is bored while waiting anymore, and empty time is always put to good use.

This universal devotion to mobile devices provides pediatricians with an opportunity to encourage our patients to improve their health and comply with recommendations. In this installment of Pediatrics V2.0 we'll detail several of the many medical devices that interface with smartphones. It's truly amazing how many of these affordable gadgets are now available, and how many more are in development and will be released in the near future.

Computers in disguise

What makes smartphones so "smart" is that they are not just phones; they are powerful portable computers that retrieve or transmit information via telephone or wireless networks. Best of all, smartphones are affordable and integrate seamlessly with other computers and smart devices we possess. This makes smartphones an ideal physician assistant for encouraging patients to follow our recommendations. For example, an overweight teenager may be less than motivated to modify his or her diet and exercise following a conversation with a pediatrician. This may be an entirely different story when the adolescent is informed that "there is an app for that" and a new affordable gadget will help him or her reach specific goals.

The "gamification" of health care is the latest strategy for motivating pediatric patients and their parents to make efforts to adopt a healthier lifestyle.

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Gamification is driven by data collection and interpretation. Patients use applications and monitoring devices to document compliance with treatment regimens and to visualize progress and goals achieved. As gamification of medical care evolves, we are likely to see patients rewarded for success by insurance companies with cash incentives, reduction in medical care premiums, or other tangible incentives.

New opportunity for diabetes care

One of the best examples of smartphone and medical-device integration is the iBGStar glucose monitoring system from Sanofi-Aventis (Bridgewater, New Jersey). This is a 2-inch-long device that plugs into the bottom of the iPhone and integrates with the iBGStar application. A test strip is inserted into the device and a drop of blood is applied. The patient is rewarded with a snazzy animation as the device calculates the blood glucose and the application displays the result. One can review previous readings and use the application to monitor for trends. The application also lets your diabetic patient input carb counts and insulin dosages. The data displayed in the application clearly illustrates the effect these have on the patient's readings. Best of all, the user can share the log of information with a nutritionist or medical provider by e-mail. The device is very affordable at $99.

iBGStar: Plug-in meter integrates with the iPhone to test blood glucose.

Other smartphone-integrated glucose meters are or will soon be available and provide different connectivity options. The Telcare BGM (Telcare; Concord, Massachusetts), the company's very popular $150 glucose meter, currently features phone network connectivity and uploads all readings inconspicuously to the cloud. Data can be accessed via the MyTelcare.com Web portal and the data syncs with a smartphone application. Via the Web portal, trends can be reviewed and printed, and the device even reminds users when it's time to order supplies.

LifeScan Inc (Milpitas, California), which markets a full line of sophisticated glucometers, recently received US Food and Drug Administration clearance to market its OneTouch VerioSync Blood Glucose Monitoring System that will connect to smartphones and tablets via Bluetooth. It is likely to be available by the time you read this.

Getting fit

Over one-third of children in the United States are either overweight or obese, and pediatricians try to encourage overweight children to modify their lifestyle via adoption of healthy eating habits and regular exercise. Mobile technologies have made it possible to gamify fitness and motivate children who welcome competition with friends and interaction with computers.

A very popular kid-oriented mobile fitness device is the Zamzee Activity Meter (Zamzee Co; Redwood City, California). Parents can purchase the mobile device for $30 and "skin" it with appealing designs and colors. The device is clipped to a belt or shoelaces. At intervals, the meter is plugged into a computer via the USB port and the upload-

Zamzee Activity Meter: Monitors activity and uploads fitness milestones to a child-friendly portal.

ed data is reviewed via a child-friendly Zamzee portal. Children earn points and badges based on goals and can level up when milestones are achieved. Motivation can also be augmented with rewards parents can purchase for children. These can be redeemed at the Zamzee online reward store or can be exchanged for gift cards to Amazon, iTunes, GameStop, and many others. According to the Web site, the effectiveness of the Zamzee device has been studied in more than 448 children over a 6-month period and its use is associated with an average activity increase of 60% compared with non-Zamzee users.

Teenaged patients really like stylish "kicks" (aka sneakers or shoes) and those who are interested in getting fit might be interested in Nike's full line of smartphone-connectible activity-monitoring products. These include a wireless sensor that fits in a special pouch in the heel of the Nike+ line of sports shoes and communicates wirelessly with an iPad Nano (via a special receiver) or smartphone; a GPS/activity-monitoring watch that plugs into a computer's USB port; and the new FuelBand system that connects to smartphones via Bluetooth. Prices range from $30 for the sports kits that include a sensor and receiver for an iPod Nano, to $150 for the FuelBand system, to $169 for the Nike+ SportsWatch GPS. All data can be viewed via an application on a smartphone or via the Nike+ Web portal.

In addition to the activity monitors just described, dozens of other fitness-monitoring systems are available. These keep track of distances traveled, calories burned, and many also track other important fitness parameters such as heart rate while exercising and duration and quality of sleep. Time will tell if these ultimately will prove worthwhile for patients who wish to lose weight or improve their level of fitness.

Another interesting device that could potentially facilitate weight loss is the Hapifork, soon to be available from Hong Kong-based Hapilabs Ltd. The device teaches patients to eat at a slower pace. If food is consumed too rapidly, the device vibrates and flashes to warn the user to slow the pace of eating. The device connects to a smartphone via Bluetooth or uploads data to your computer via USB, then syncs with the Hapilabs Online Dashboard, a Web portal that keeps track of how long a meal takes as well as the number of fork servings per meal and the interval between bites. The device comes in a number of appealing colors and can be cleaned in a dishwasher. Many are optimistic that this simple device will make a profound difference in assisting our obese patients to pace themselves during mealtime, so satiety is achieved before overeating occurs. As of this writing, the price of the Hapifork has not been set.

Smart Baby Monitor: Transmits high-resolution video and sound for viewing on a smartphone.

Lastly, Withings.com markets a full line of affordable smartphone-integrated products to help parents monitor the health and well-being of their children. The company sells a full-featured baby monitor that transmits high-resolution video and sound over a wireless network, phone network, or Bluetooth so parents can view their baby on a smartphone anywhere and anytime. Parents can talk with their baby, play a lullaby, and be alerted when the baby cries or fusses. The baby monitor sells for $250. Withings also markets a baby scale that syncs via a wireless network or Bluetooth with computers and smart devices. The app keeps track of feedings and plots the child's weight gain on gender-specific growth

Smart Kid Scale: Syncs with smart devices and plots weight gain on gender-specific growth charts.

charts. The baby scale is $180, and converts to a child scale simply by removing the cradle.

Withings also sells a $150 fitness scale that monitors weight, body mass index, and heart rate, as well as a smartphone-connected sphygmomanometer. The $129 sphygmomanometer helps patients monitor their blood pressure readings and the effect that medication, diet, and exercise have on improving blood pressure. Data can be shared with providers via e-mail or via a secure patient portal.

Breathing easier

Several mobile devices can assist parents in the home monitoring of children with respiratory problems. For many children, peak flow meters are used to monitor respiratory status, and many smartphone applications such as Asthma Buddy, Asthma MD, and asthmaTrack can be used to track peak flow reading scores, medication use, and exacerbations. Pulse oximeters have come down in price significantly and several are now being sold in pharmacies for as little as $40. These can determine whether an asthma exacerbation is associated with a falling pulse oximeter reading and thus warrants an expedited medical evaluation. The iSpO2 from Masimo (Irvine, California) is the first iPhone-connectible pulse oximeter. It has a special application that displays the pulse oximeter reading along with the pulse and the perfusion index and keeps a log of readings so these can be reviewed with physicians to guide therapy. The device sells for $250.

Fitness scale: Monitors weight, body mass index, and heart rate in one step.

Asthmapolis (Madison, Wisconsin) is releasing an innovative sensor that fits atop standard controller and rescue inhalers and syncs with a mobile app via Bluetooth. By using the Asthmapolis sensor, patients will be able to provide their physicians with information that documents compliance with controller meds as well as the frequency and location (via GPS) of rescue medication usage. Previously, physicians had to depend on patient and parent reports regarding compliance and exacerbations. The use of the new device and its ability to present objective data may facilitate creation of new personalized strategies for improving asthma management.

Lastly, iSonea Ltd (Melbourne, Australia) manufactures a handheld acoustic monitor called the Wheezometer for documenting asthma symptoms in patients. The device analyzes a 30-second record of a child's respiratory noises and produces a measurement called the WheezeRATE. The device is being promoted as an adjunct to oximetry, peak flows, and asthma scoring as a means to document the presence of asthma symptoms and response to therapy, both long-term and during acute exacerbations. The company has also announced that it anticipates the production of a new smartphone-connected

We now have the ability to encourage patients to use smartphone-connected devices to lose weight, exercise regularly, and adhere to our recommendations for management of obesity, diabetes, asthma, and hypertension.

AirSonea system before the end of this year. The system will link a new version of its respiratory acoustic monitor to a smartphone application that displays the device's readings.

In the office

Patients are intrigued by all the medical gadgets and gizmos we use in the medical office, and they may be even more interested if you integrate mobile devices into your own practice. The advantage of doing so is that the mobile applications excel at showing patients the significance of measurements. If we show patients that we feel mobile devices are accurate and reliable enough for office use, we encourage patients and parents to consider using mobile health technology at home when indicated.

AliveCor Heart Monitor: The device enables a smartphone to record a single-lead electrocardiogram.

Of the devices mentioned above, smartphone- or iPod touch-connected glucose meters, pulse oximeters, blood pressure cuffs, and wireless scales and baby scales provide affordable alternatives to our standard office devices. In addition to these, you might also be interested in purchasing a few others that either are presently available or will soon be available.

AliveCor (San Francisco, California) offers a $200 heart monitor that snaps on an iPhone and enables the smartphone to function as a single-lead electrocardiogram (ECG) recorder. The device is either held by the fingers of both hands or placed on a patient's chest, and the device displays the ECG along with the heart rate. The device can display a continuous ECG and record up to 30 seconds of a rhythm strip that can be captured and electronically transferred via the cloud. Although not a substitute for a Holter monitor, the device is capable of capturing abnormal rhythms in patients you suspect may have a dysrhythmia on auscultation or via a pulse check.

Another device that may be available by the time you read this article is the Remotoscope from CellScope Inc (San Francisco, California), now in development. An attachment to a typical smartphone gives the user the ability to visualize and photograph the tympanic membrane in high resolution. If the optics are as good as I expect, I see the Remotoscope being a useful tool in educating parents about the diagnosis and treatment of otitis media or otitis externa.

Where do we go from here?

Clearly a new age of mobile medical gadgetry is in its infancy and evolving rapidly. We now have the ability to encourage patients to use smartphone-connected devices to lose weight, exercise regularly, and adhere to our recommendations for management of obesity, diabetes, asthma, and hypertension. These devices also provide your practice with the opportunity to gamify some aspects of health care, improving the likelihood that children may adopt a healthier lifestyle. CP

PROFESSIONAL MESSAGES

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CALENDAR

JUNE

18-20: 7th Biennial Childhood Obesity Conference.
Long Beach, California.
CONTACT: California Department of Public Health, www.childhoodobesity2013.com

27-28: 4th International Conference on Pediatric Abusive Head Trauma.
Burlington, Vermont.
CONTACT: Penn State Hershey College of Medicine, www.pennstatehershey.org/web/aht/home

JULY

10-13: 15th Annual Summer Conference on Pediatrics.
Napa, California.
CONTACT: Symposia Medicus, www.symposiamedicus.org/assets/conference/1261/1261.html

22-24: Pediatric and Adult Infectious Diseases: An Evidence-Based Approach to Common Problems (CME).
Anaheim, California.
CONTACT: MCE Conferences, www.mceconferences.com/conference-detail.php?conf_id=PN939-6-5-19-32

28-2: 31st Annual Conference on Pediatric Infectious Diseases.
Vail, Colorado.
CONTACT: Children's Hospital Colorado, www1.childrenscolorado.org/Events/calendar-detail/?eventId=c52e487c-7571-e211-8f54-2c768a4e1b84

AUGUST

1-4: Pediatric Hospital Medicine Conference.
New Orleans, Louisiana.
CONTACT: American Academy of Pediatrics, www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Section-on-Hospital-Medicine/Pages/Pediatric-Hospital-Medicine-2012.aspx

24-29: International Congress of Pediatrics 2013.
Melbourne, Australia.
CONTACT: International Pediatric Association, www2.kenes.com/IPA/Pages/home.aspx

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/

25-28: Current Concepts in Neonatal Care.
Napa, California.
CONTACT: Symposia Medicus, http://symposiamedicus.org/assets/conference/1258/1258.html

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.pediatricshawaii.com

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

7-10: 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/

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/

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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.

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