Supplement to
INFECTIOUS DISEASES IN CHILDREN®

OCTOBER 2016

Recent Highlights in ADHD

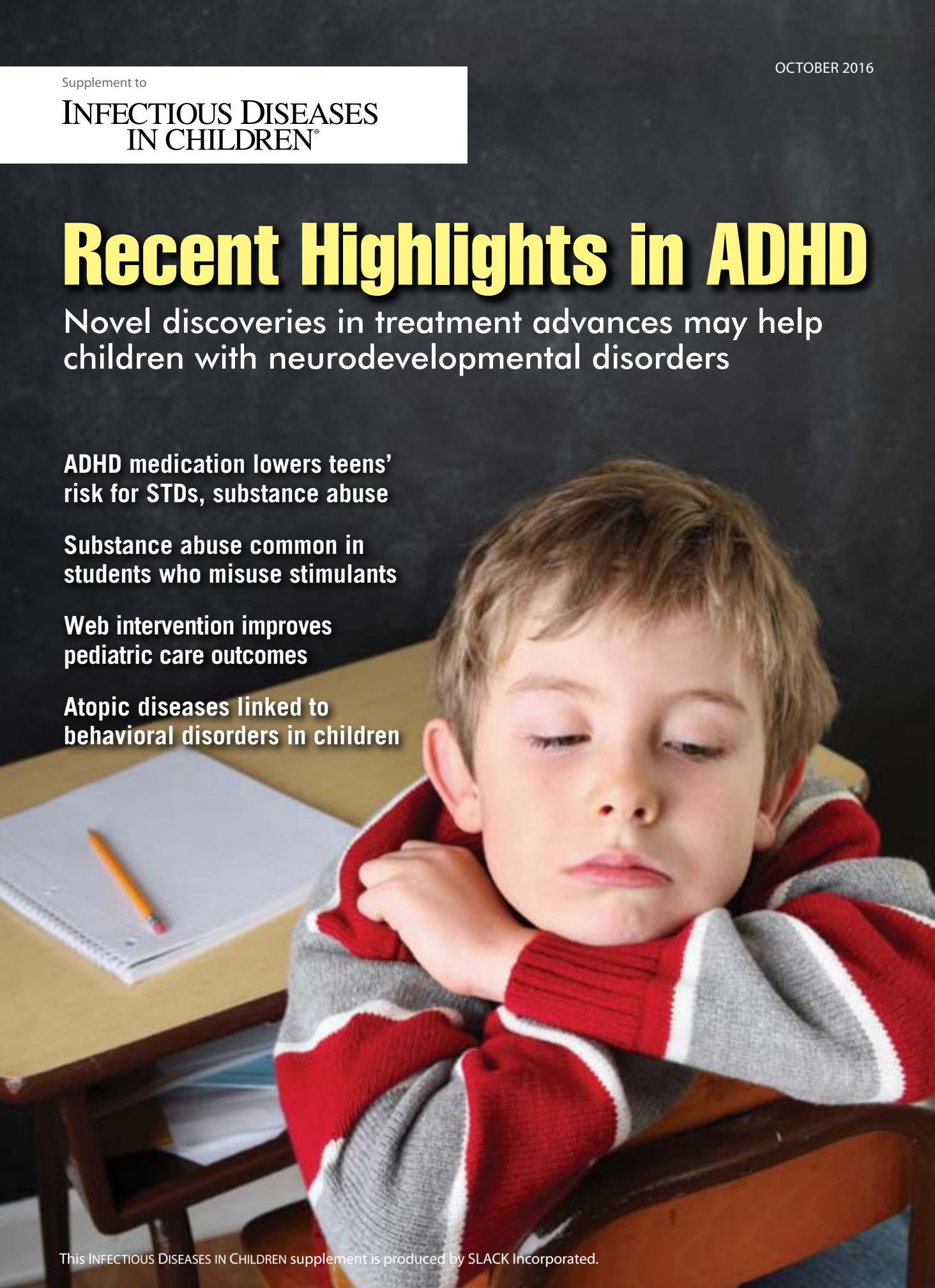
Novel discoveries in treatment advances may help children with neurodevelopmental disorders

ADHD medication lowers teens' risk for STDs, substance abuse

Substance abuse common in students who misuse stimulants

Web intervention improves pediatric care outcomes

Atopic diseases linked to behavioral disorders in children



This INFECTIOUS DISEASES IN CHILDREN supplement is produced by SLACK Incorporated.

INDICATION AND LIMITATION OF USE

For the treatment of ADHD (ages ≥6 years). Vyvanse is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. Safety and effectiveness of Vyvanse for the treatment of obesity have not been established.

Vyvanse® may help control **ADHD** in your patients ages 6-12

Important Safety Information

WARNING: ABUSE AND DEPENDENCE

- **CNS stimulants (amphetamines and methylphenidate-containing products), including Vyvanse, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing; monitor for signs of abuse and dependence during therapy.**

- **Contraindications**

Patients should not take Vyvanse if they are:

- hypersensitive to amphetamines or other ingredients of Vyvanse. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have occurred.
- taking monoamine oxidase inhibitors (MAOI) or have taken an MAOI within the past 14 days. Hypertensive crisis can occur.

- **Warnings and Precautions**

- Prior to and during treatment assess for the presence of cardiac disease. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Note that sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulants at recommended doses, as well as sudden death in children and adolescents with structural cardiac abnormalities and other serious heart problems while taking CNS stimulants at recommended doses. Evaluate patients with exertional chest pain, unexplained syncope, or arrhythmias while taking Vyvanse.
- CNS stimulants can cause increases in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for tachycardia and hypertension.
- Prior to treatment assess for the presence of bipolar disorder. CNS stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis.
- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Monitor weight and height in children during treatment with Vyvanse. Treatment may need to be interrupted in children not growing as expected.
- CNS stimulants, including Vyvanse, are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; very rare sequelae include digital ulceration and/or soft tissue breakdown. Observe patients for new numbness, pain, skin color change, or sensitivity to temperature in fingers and toes. Further evaluation may be required, including referral.

- **Adverse Reactions**

The most common adverse reactions (≥5% and at least twice the rate of placebo) reported in clinical trials were:

- *Children aged 6 to 12:* decreased appetite, insomnia, upper abdominal pain, irritability, vomiting, decreased weight, nausea, dry mouth, and dizziness;
- *Adolescents aged 13 to 17:* decreased appetite, insomnia, and decreased weight;
- *Adults:* decreased appetite, insomnia, dry mouth, diarrhea, nausea, anxiety, and anorexia.

Please see Brief Summary of Full Prescribing Information on following pages.

VYVANSE PROVIDED CONSISTENT EFFICACY IN PEDIATRIC PATIENTS WITH ADHD AT EACH TIMEPOINT MEASURED, FROM 1.5 TO 13 HOURS POSTDOSE[1]

PRIMARY ENDPOINT

SKAMP-D time of onset[2]

- **1.5 hours** postdose: LS (least squares) mean SKAMP-D score of **.70** for Vyvanse vs **1.14** for placebo (*P*<.005)

KEY SECONDARY ENDPOINT

SKAMP-D duration of efficacy[2,3]

- Significant improvement in LS mean SKAMP-D scores for Vyvanse vs placebo at all postdose timepoints measured: **1.5 hr** (0.70 vs 1.14); **2.5 hr** (0.45 vs 1.42); **5 hr** (0.44 vs 1.60); **7.5 hr** (0.54 vs 1.56); **10 hr** (0.60 vs 1.43); **12 hr** (0.90 vs 1.41); **13 hr** (1.05 vs 1.31); *P*<.005 for all postdose timepoints

SKAMP-D (Swanson, Kotkin, Agler, M-Flynn, and Pelham Deportment) subscale is a validated, standardized classroom assessment tool that measures behavior problems leading to classroom disruptions. It is not a measure of classroom or academic performance. Lower scores indicate less severe symptoms.

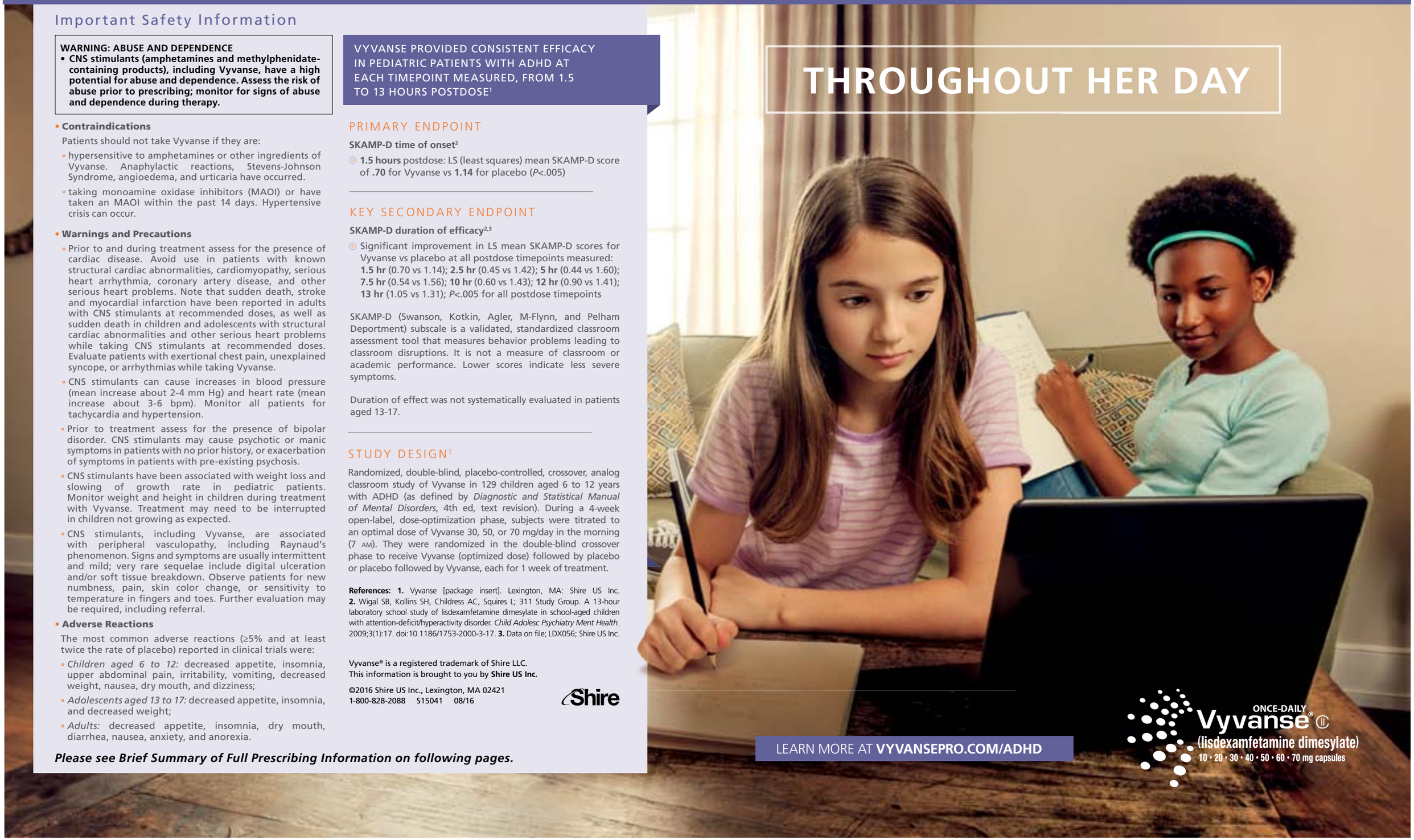
Duration of effect was not systematically evaluated in patients aged 13-17.

STUDY DESIGN[1]

Randomized, double-blind, placebo-controlled, crossover, analog classroom study of Vyvanse in 129 children aged 6 to 12 years with ADHD (as defined by *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, text revision). During a 4-week open-label, dose-optimization phase, subjects were titrated to an optimal dose of Vyvanse 30, 50, or 70 mg/day in the morning (7 AM). They were randomized in the double-blind crossover phase to receive Vyvanse (optimized dose) followed by placebo or placebo followed by Vyvanse, each for 1 week of treatment.

References: 1. Vyvanse [package insert]. Lexington, MA: Shire US Inc. **2.** Wigal SB, Kollins SH, Childress AC, Squires L; 311 Study Group. A 13-hour laboratory school study of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatry Ment Health*. 2009;3(1):17. doi:10.1186/1753-2000-3-17. **3.** Data on file; LDX056; Shire US Inc.

Shire



VYVANSE® (lisdexamfetamine dimesylate) Capsules

10, 20, 30, 40, 50, 60, 70 mg CII Rx Only

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

WARNING: ABUSE AND DEPENDENCE

CNS stimulants (amphetamines and methylphenidate-containing products), including VYVANSE, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

INDICATIONS AND USAGE

VYVANSE® is indicated for treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Limitation of Use:

VYVANSE is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established.

DOSAGE AND ADMINISTRATION

- Initial Dose: 30 mg every morning in patients ages 6 and above
- Titration Schedule: 10 mg or 20 mg weekly
- Recommended Dose: 30 mg to 70 mg per day
- Maximum Dose: 70 mg per day
- Prior to treatment, assess for presence of cardiac disease
- Severe renal impairment: Maximum dose is 50 mg/day
- End stage renal disease (ESRD): Maximum dose is 30 mg/day

CONTRAINDICATIONS

VYVANSE is contraindicated in patients with:

- Known hypersensitivity to amphetamine products or other ingredients of VYVANSE. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports.
- Concurrent administration of monoamine oxidase inhibitors (MAOI) or administration of VYVANSE within 14 days of the last MAOI dose. Hypertensive crisis can occur.

WARNINGS AND PRECAUTIONS

Potential for Abuse and Dependence *(See Boxed Warning Above)*

Serious Cardiovascular Reactions

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

Blood Pressure and Heart Rate Increases

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

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 mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode.

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing VYVANSE. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in 0.1% of CNS stimulant-treated patients compared to 0% in placebo-treated patients.

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 VYVANSE. In a 4-week, placebo-controlled trial of VYVANSE in patients ages 6 to 12 years old with ADHD, there was a dose-related decrease in weight in the VYVANSE groups compared to weight gain in the placebo group. Additionally, in studies of another stimulant, there was slowing of the increase in height.

Peripheral Vasculopathy, including Raynaud's Phenomenon

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

ADVERSE REACTIONS

Clinical Trial Experience

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

The safety data in this section is based on data from 4-week parallel-group controlled clinical studies of VYVANSE in pediatric and adult patients with ADHD.

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials

In the controlled trial in patients ages 6 to 12 years, 9% (20/218) of VYVANSE-treated patients discontinued due to adverse reactions compared to 1% (1/72) of placebo-treated patients. Most frequent adverse reactions leading to discontinuation (i.e. leading to discontinuation in at least 1% of VYVANSE-treated patients and at a rate at least twice that of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, and rash [2 instances for each adverse reaction, i.e., 2/218 (1%)].

In the controlled trial in patients ages 13 to 17 years, 4% (10/233) of VYVANSE-treated patients discontinued due to adverse reactions compared to 1% (1/77) of placebo-treated patients. Most frequent adverse reactions leading to discontinuation were irritability (3/233; 1%), decreased appetite (2/233; 1%), and insomnia (2/233; 1%).

In the controlled adult trial, 6% (21/358) of VYVANSE-treated patients discontinued due to adverse reactions compared to 2% (1/62) of placebo-treated patients. Most frequent adverse reactions leading to discontinuation (i.e. leading to discontinuation in at least 1% of VYVANSE-treated patients and at a rate at least twice that of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%).

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in children, adolescents, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or More Among VYVANSE-Treated Patients with ADHD in Clinical Trials

Adverse reactions reported in the controlled trials in pediatric patients ages 6 to 12 years, adolescent patients ages 13 to 17 years, and adult patients treated with VYVANSE or placebo are presented in Tables 1, 2, and 3 below.

Table 1 Adverse Reactions Reported by 2% or More of Children (Ages 6 to 12 Years) with ADHD Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial

	VYVANSE (n=218)	Placebo (n=72)
Decreased Appetite	39%	4%
Insomnia	23%	3%
Abdominal Pain Upper	12%	6%
Irritability	10%	0%
Vomiting	9%	4%
Weight Decreased	9%	1%
Nausea	6%	3%
Dry Mouth	5%	0%
Dizziness	5%	0%
Affect lability	3%	0%
Rash	3%	0%
Pyrexia	2%	1%
Somnolence	2%	1%
Tic	2%	0%

Table 2 Adverse Reactions Reported by 2% or More of Adolescent (Ages 13 to 17 Years) Patients with ADHD Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial

	VYVANSE (n=233)	Placebo (n=77)
Decreased Appetite	34%	3%
Insomnia	13%	4%
Weight Decreased	9%	0%
Dry Mouth	4%	1%

Table 3 Adverse Reactions Reported by 2% or More of Adult Patients with ADHD Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial

	VYVANSE (n=358)	Placebo (n=62)
Decreased Appetite	27%	2%
Insomnia	27%	8%
Dry Mouth	26%	3%
Diarrhea	7%	0%
Nausea	7%	0%
Anxiety	6%	0%
Anorexia	5%	0%
Feeling Jittery	4%	0%
Agitation	3%	0%
Increased Blood Pressure	3%	0%
Hyperhidrosis	3%	0%
Restlessness	3%	0%
Decreased Weight	3%	0%
Dyspnea	2%	0%
Increased Heart Rate	2%	0%
Tremor	2%	0%

In addition, in the adult population erectile dysfunction was observed in 2.6% of males on VYVANSE and 0% on placebo; decreased libido was observed in 1.4% of subjects on VYVANSE and 0% on placebo.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of VYVANSE. 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 events are as follows: palpitations, cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, tics, bruxism, depression, dermatillomania, aggression, Stevens-Johnson Syndrome, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, constipation, and rhabdomyolysis.

DRUG INTERACTIONS

Clinically Important Interactions with VYVANSE

Effect of Other Drugs on VYVANSE

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Acidifying and Alkalinizing Agents	Ascorbic acid and other agents that acidify urine increase urinary excretion and decrease the half-life of amphetamine. Sodium bicarbonate and other agents that alkalinize urine decrease urinary excretion and extend the half-life of amphetamine.	Adjust the dose accordingly

Effect of VYVANSE on Other Drugs

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Monoamine Oxidase Inhibitors (MAOIs)	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.	Do not administer VYVANSE concomitantly or within 14 days after discontinuing MAOI treatment

Drugs Having No Clinically Important Interactions with VYVANSE

From a pharmacokinetic perspective, no dose adjustment of VYVANSE is necessary when VYVANSE is co-administered with guanfacine, venlafaxine, or omeprazole. In addition, no dose adjustment of guanfacine or venlafaxine is needed when VYVANSE is co-administered.

From a pharmacokinetic perspective, no dose adjustment for drugs that are substrates of CYP1A2 (e.g. theophylline, duloxetine, melatonin), CYP2D6 (e.g. atomoxetine, desipramine, venlafaxine), CYP2C19 (e.g. omeprazole, lansoprazole, clobazam), and CYP3A4 (e.g. midazolam, pimozide, simvastatin) is necessary when VYVANSE is co-administered.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C: Risk Summary

There are no adequate and well-controlled studies with VYVANSE in pregnant women. VYVANSE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Amphetamines are excreted into human milk. Long-term neuro-developmental effects on infants from amphetamine exposure are unknown. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness have been established in pediatric patients with ADHD ages 6 to 17 years. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

Geriatric Use

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

Renal Impairment

Due to reduced clearance in patients with severe renal impairment (GFR 15 to <30 mL/min/1.73 m^2), the maximum dose should not exceed 50 mg/day. The maximum recommended dose in ESRD (GFR <15 mL/min/1.73 m^2) patients is 30 mg/day.

Lisdexamfetamine and d-amphetamine are not dialyzable.

Gender

No dosage adjustment of VYVANSE is necessary on the basis of gender.

DRUG ABUSE AND DEPENDENCE

VYVANSE contains lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.

OVERDOSAGE

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdosage. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Lisdexamfetamine and d-amphetamine are not dialyzable.

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421
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Recent research identifies novel benefits, risks related to the use of ADHD medication

The CDC and National Institute of Mental Health have previously reported that the prevalence of neurodevelopmental disorders in children and adolescents has increased over the past several decades. The likely |continued increase in diagnoses has led physicians and researchers to analyze the risks and benefits associated with current treatment options.

Recent research demonstrates that the use of pharmacological agents for attention-deficit/hyperactivity disorder significantly reduces the probability of adolescents contracting STDs, abusing drugs and alcohol, and becoming injured.

In addition, novel advances identified that the combination of d-methylphenidate and guanfacine was more effective for the treatment of ADHD than either therapy alone.

Studies have also helped to identify behaviors and risk factors that may help in diagnosing ADHD.

The results of a cross-sectional analysis of 100 college students who misused stimulants and 198 students who did not, demonstrated that students who misused prescription stimulants were more likely to have conduct disorders, as well as substance use disorder.

This supplement, brought to you by the publishers of INFECTIOUS DISEASES IN CHILDREN, highlights the most up-to-date research on novel discoveries in ADHD. In addition, results of a cross-sectional analysis of

For additional headlines on the treatment of children with mental health disorders, visit Healio.com/Pediatrics.
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WEB WATCH

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Acetaminophen use during pregnancy linked to children's behavioral issues

Children exposed to acetaminophen through maternal consumption during pregnancy were at an increased risk for developing difficult behavioral symptoms. To read this article, and the full articles summarized below, please visit Healio.com/Pediatrics.

Internet addiction linked to functional impairment in college students

College students who screened positively for internet addiction had higher levels of depression and anxiety, attentional problems and ADHD symptoms.

"We found that those screening positive on the [Internet Addiction Test] as well as on our scale, had significantly more trouble dealing with their day to day activities, including life at home, at work/school and in social settings," a study researcher said in a press release.

Unhealthy diet during pregnancy linked to behavioral disorders in youth

Recent findings published in the Journal of Child Psychology and Psychiatry suggest that maintaining a healthy diet while pregnant may reduce the risk for ADHD symptoms in early-onset persistent youth.

"One prenatal risk that is a correlate of these psychosocial risks, yet has received far less attention, is diet," the researchers wrote. "'Unhealthy diet' (eg, high fat/sugar) is of particular interest as it has been reported to associate with … [conduct problems]."

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Originally posted on Healio.com/Psychiatry | August 5, 2016

Methylphenidate affects dopaminergic system in children, not adults

Recent findings indicated treatment with methylphenidate for attention-deficit/hyperactivity disorder significantly affected the dopaminergic system in children but not adults.

"Safety investigations on the effects of methylphenidate on [extracellular dopamine] function in the developing brain are scarce in children. Regardless of this alarming paucity of findings, increasingly greater numbers of children and young adolescents are exposed to methylphenidate, many of whom likely do not meet the criteria for ADHD. This heightened use has led to considerable debate and concern (eg, among parents) about the long-term consequences or possible adverse effects of methylphenidate use in children," **Anouk Schrantee, MSc**, of University of Amsterdam, and colleagues wrote. "Such knowledge is urgently needed, as recently emphasized by several entities, including the FDA, NIH and the European Committee for Medicinal Products for Human Use."

To determine age-dependent effects of methylphenidate on the dopaminergic system, researchers conducted a randomized, double-blind, placebo-controlled trial among 50 stimulant treatment-naïve boys, aged 10 to 12 years, and 49 stimulant treatment-naïve men, aged 23 to 40 years diagnosed with ADHD. Study participants received methylphenidate or placebo for 16 weeks.

Methylphenidate increased cerebral blood flow treatment response in the thalamus among children but not adults, with a mean difference of 6.5 (95% CI, 0.4-12.6; $P = .04$).

Striatal cerebral blood flow was significantly higher among children who received methylphenidate, compared with placebo (mean difference = 7.7; 95% CI, 0.7-14.8; $P = .03$). This effect was not observed among adults.

"In line with extensive preclinical data, we provide the first evidence, to our knowledge, that methylphenidate treatment during a specific period of maturation alters the [cerebral blood flow] response, likely reflecting increased [extracellular dopamine] neurotransmission due to neurochemical imprinting by methylphenidate. In the short term, these alterations do not induce major benefits or harm regarding clinical improvement, but the long-term consequences remain to be established. Therefore, our data stress the need for longer follow-up studies that address possibly progressive disturbances of the [extracellular dopaminergic] system and associated behavioral abnormalities," the researchers concluded.
– by Amanda Oldt ■

"... our data stress the need for longer follow-up studies that address possibly progressive disturbances of the [extracellular dopaminergic] system and associated behavioral abnormalities."
ANOUK SCHRANTEE, MSC

Reference:
Schrantee A, et al. *JAMA Psychiatry.* 2016;doi:10.1001/jamapsychiatry.2016.1572.

Disclosures: Schrantee reports no relevant financial disclosures. Please see the full study for a list of all authors' relevant financial disclosures.

Originally posted on Healio.com/Psychiatry | August 8, 2016

Combination therapy more effective than monotherapy for ADHD

A combination of d-methylphenidate and guanfacine was more effective for attention-deficit/hyperactivity disorder than either treatment alone, according to recent findings.

"The discordance between symptom reduction from standard treatments and continued impaired functioning long term highlights the importance of identifying treatments that better remediate proximal causes of negative outcomes."

— JAMES T. MCCRACKEN, MD

"Despite symptom reduction with monotherapies, there is little evidence to show that medications change long-term trajectories of either symptoms or academic, psychiatric, and social outcomes, although some acute and follow-up studies find modest academic gains. The discordance between symptom reduction from standard treatments and continued impaired functioning long term highlights the importance of identifying treatments that better remediate proximal causes of negative outcomes," **James T. McCracken, MD**, of the David Geffen School of Medicine at University of California, Los Angeles, and colleagues wrote.

To compare efficacy of extended-release d-methylphenidate, a combined dopamine and noradrenergic agonist, with guanfacine, an 2A receptor agonist, researchers conducted an 8-week randomized, double-blind, comparative trial among 207 children aged 7 to 14 years with DSM-IV ADHD. Study participants received guanfacine at 1 mg to 3 mg per day, d-methylphenidate at 5 mg to 20 mg per day, or a combination with fixed flexible dosing.

Overall, there were significant treatment group main effects for ADHD Rating Scale IV (ADHD-RS-IV) ADHD total ($P = .0001$) and inattentive symptoms ($P = .0001$).

Participants who received combination therapy had small but consistently greater reductions in ADHD-RS-IV inattentive subscale scores compared with monotherapy of d-methylphenidate ($P = .05$) or guanfacine ($P = .02$).

Combination therapy was associated with a greater positive response rate indicated by Clinical Global Impression Improvement scores ($P = .01$).

No serious cardiovascular events occurred.

Sedation, somnolence, lethargy and fatigue were more common in the guanfacine group.

All treatments were well-tolerated, according to researchers.

"Results from our study suggest modest but consistent additional benefit from a carefully applied combination of a psychostimulant with a selective 2A agonist, guanfacine, on ADHD symptoms and global clinical responses. Our findings should also serve to encourage further research to identify a range of treatment strategies using other possible approaches to successfully improve the long-term trajectory of ADHD," the researchers concluded.

– by Amanda Oldt ■

Reference:
McCracken JT, et al. *J Am Acad Child Adolesc Psychiatry.* 2016;doi:10.1016/j.jaac.2016.05.015.

Disclosures: McCracken reports receiving consultant honoraria from Dart Neuroscience and Think Now Inc. Please see the full study for a list of all authors' relevant financial disclosures.

Originally published on Healio.com/Pediatrics | August 29, 2016

ADHD medication lowers teens' risk for STDs, substance abuse, injuries

Pharmacological treatment for attention-deficit/hyperactivity disorder significantly reduced the probability of adolescents contracting STDs, abusing drugs and alcohol, and becoming injured, according to recent research.

"ADHD is such a major issue, but no one seemed to be able to give a very definite answer to the long-term effect of the medication," **Anna Chorniy, PhD,** of the Center for Health and Wellbeing at Princeton University, who conducted the research with Leah Kitashima, said in a press release. "For our sample population, we were able to see everyone who had an ADHD diagnosis and track their health over time to identify any potential benefits of the medication or lack thereof."

"ADHD is such a major issue, but no one seemed to be able to give a very definite answer to the long-term effect of the medication."

— ANNA CHORNIY, PHD

The researchers used a panel of South Carolina Medicaid claims data from 2003 to 2013 to investigate the pharmacological treatment effects on 150,000 children diagnosed with ADHD. Chorniy and Kitashima specifically evaluated medication effects on the probability of risky sexual behavior outcomes, including pregnancy and STDs, substance abuse disorders and injuries, and followed physicians' preferences to prescribe medications.

The investigation results indicated a strong correlation between ADHD medication use and the reduced probability and severity of short-term and long-term negative health results. In the 10-year analysis, children with ADHD who received pharmacological treatment were 3.6 percentage points less likely to be treated for an STD, 5.8 percentage points less likely to be screened for an STD and 7.3 percentage points less likely to need treatment for substance abuse vs. children who did not receive pharmacological treatment. Boys were less likely than girls to be treated (12 percentage points) or screened (25 percentage points) for an STD, but more likely to receive medical attention for drug and alcohol abuse (4.1 percentage points). In addition, the study analysis indicated that pharmacological treatment is associated with decreases in the following areas: probability of contracting an STD (1.1 percentage points); probability of being screened for an STD (1.9 percentage points); probability of abusing alcohol or drugs (1.8 percentage points); and probability of being injured (2.3 percentage points).

"Over the past decade, SC Medicaid spending on prescription drugs increased nearly threefold to $69 million in 2013," Chorniy and Kitashima wrote. "It is important to understand whether the increased expenditures on treatment produced any benefit in terms of improved health (fewer and less injuries), reduction in risky behaviors that potentially lead to teen pregnancies, STDs and substance use and abuse."

– by Kate Sherrer ■

Reference:
Chorniy A, Kitashima L. *Labour Econ.* 2016;doi:10.1016/j.labeco.2016.06.014.

Disclosure: Chorniy and Kitashima report no relevant financial disclosures.

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ADHD, conduct disorder common in students who misuse stimulants

College students who misused prescription stimulants were more likely to have attention-deficit/hyperactivity disorder, conduct disorder, substance use disorder and overall dysfunction, according to recent findings.

"Our data suggest that college students who misuse prescription stimulant medications are more likely to exhibit clinically relevant psychiatric dysfunction," **Timothy Wilens, MD,** chief of child and adolescent psychiatry at Massachusetts General Hospital for Children, said in a press release. "In addition to higher levels of ADHD, conduct disorder, and alcohol or drug use disorders, the majority of those misusing stimulants met or approached criteria for stimulant-use disorder."

"Our data suggest that college students who misuse prescription stimulant medications are more likely to exhibit clinically relevant psychiatric dysfunction."

— TIMOTHY WILENS, MD

To determine associations between stimulant misuse, ADHD, substance use disorders and other psychopathology among college students, researchers conducted a cross-sectional analysis of 100 college students who misused stimulants and 198 students without misuse. Study participants completed Structured Clinical Interviews for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition and self-reports. Mean age was 20.7 years.

Stimulant misusers were more likely to report alcohol, drug, alcohol and drug, and any substance use disorder ($P < .01$ for all).

Analysis of a subset of stimulant misusers indicated 67% had full or subthreshold prescription stimulant use disorder.

Stimulant misusers were more likely to have conduct disorder (10% vs. 3%; $P = .02$), ADHD (27% vs. 16%; $P = .02$), and lower Global Assessment of Functioning scores ($P < .01$), compared with those who did not misuse stimulants.

Immediate-release stimulant misuse was more common than extended-release stimulant misuse, according to researchers.

"Not everyone is driven to misuse prescription stimulants simply to 'get high.' Some misusers may be pressured to use a friend's prescription if they believe it will improve academic performance, which is not likely if combined with alcohol or other drugs," Wilens said in the release. "It's possible that pre-existing cognitive deficits may lead some individuals to develop stimulant misuse as they try to self-medicate. The extent of an actual stimulant-use disorder in those who misused stimulants at all suggests that this problem may be more prevalent and severe than previously thought. And finding in this population that immediate-release stimulants have a much higher likelihood of being misused than do extended-release stimulants emphasizes the usefulness of prescribing extended-release versions or possibly nonstimulant ADHD drugs for college students." – *by Amanda Oldt* ■

Reference:
Wilens T, et al. *J Clin Psychiatry.* 2016;doi:10.4088/JCP.14m09559.

Disclosure: Wilens reports receiving grant support from NIH, NIDA and Pfizer; serving as a consultant for Euthymics/Neurovance, NIH, NIDA, Ironshore, Sunovion, Theravance and Tris Pharma; authoring *Straight Talk about Psychiatric Medications for Kids* (Guilford Press), coediting *ADHD in Children and Adults* (Cambridge Press), *General Hospital Comprehensive Clinical Psychiatry* (Sage); co-owning a copyrighted diagnostic questionnaire (Before School Functioning Questionnaire); and holding a licensing agreement with Ironshore (BFSQ Questionnaire). Please see the full study for a list of all authors' relevant financial disclosures.

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Atopic diseases linked to ADHD in children

Children with atopic diseases such as asthma, allergic rhinitis, or eczema, and those whose parents who were exposed to attention-deficit/hyperactivity disorder and atopic disease medications, were more susceptible to developing ADHD, according to study results.

"The increased prevalence of ADHD during the past decades is also paralleled by a worldwide increase in atopic diseases. This and other arguments may point to a link between atopic diseases and ADHD," **Jurjen van der Schans, MSc,** of the department of pharmacy, pharmacoepidemiology, and pharmacoeconomics at the University of Groningen in the Netherlands, and colleagues wrote. "Currently, the etiologic pathways of the possible association between atopic diseases and ADHD are still not well understood."

The researchers utilized data from the Groningen University prescription database to analyze whether children, aged 6 to 12 years, taking ADHD medications had a higher tendency of receiving treatment for atopic diseases before initiation of those ADHD medications compared with controls.

Children prescribed methylphenidate at least twice within 12 months were classified as cases and matched to four controls based on age, sex, and regional area code. There were 4,257 cases and 17,028 matched controls identified in the retrospective cohort study.

"The increased prevalence of ADHD during the past decades is also paralleled by a worldwide increase in atopic diseases."

JURJEN VAN DER SCHANS, MSC

Parents taking ADHD and atopic disease drugs were evaluated to determine the influence of ADHD medication use in their children. Parental prescription data were analyzed for relationships between cases and controls.

Results showed that cases were more likely to be treated for asthma (adjusted OR = 1.4; 95% CI, 1.3-1.6), allergic rhinitis (aOR = 1.4; 95% CI, 1.1-1.8) and eczema (aOR = 1.3; 95% CI, 1.1-1.5) compared with controls. Parents receiving medications for asthma (aOR = 1.2; 95% CI, 1.1-1.3) and allergic rhinitis (aOR = 1.3; 95% CI, 1.1-1.5) and ADHD (aOR = 3.8; 95% CI, 3.3-4.3) increased the risk for ADHD treatment in their offspring, suggesting a probable genetic or shared environmental factor.

"Our study provides additional evidence to support the hypothesis that atopic disorders, such as asthma, increase the risk of developing ADHD," van der Schans and colleagues concluded. "This evidence could indicate that there is a link between atopy and ADHD or that certain patients are more prone to health care-seeking behavior and therefore more likely to receive atopy and ADHD medication." – *by Alaina Tedesco* ■

Reference:
van der Schans J, et al. *Ann Allergy Asthma Immunol.* 2016;doi:10.1016/j.ani.2016.05.025.

Disclosure: The researchers report no relevant financial disclosures.

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Study suggests child, adult ADHD are two distinct syndromes

Recent findings indicated distinct developmental trajectories between childhood and adulthood attention-deficit/hyperactivity disorder, suggesting that the theory that adulthood attention-deficit/hyperactivity disorder is a continuation of childhood attention-deficit/hyperactivity disorder is incorrect.

"The requirement of a childhood onset has always been a key criterion for the diagnosis of attention-deficit/hyperactivity disorder (ADHD) in adults, but recently this requirement has become surrounded by controversy," **Arthur Caye**, of the Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, and colleagues wrote.

To determine if adults with ADHD symptoms always have a childhood-onset disorder, researchers analyzed data from the 1993 Pelotas Birth Cohort Study for 5,249 individuals born in Pelotas, Brazil in 1993. Study participants were followed to age 18 or 19 years, with 81.3% retention. ADHD status at age 11 years was determined via the hyperactivity subscale of the Strength and Difficulties Questionnaire adjusted for a DSM-IV ADHD diagnosis based on clinical interviews with parents using the Development and Well-Being Assessment. At age 18 to 19 years, ADHD diagnosis was determined based on DSM-5 criteria.

At age 11 years, 8.9% of the cohort had childhood ADHD. At age 18 to 19 years, 12.2% of the cohort met DSM-5 criteria for young adult ADHD, except age at onset.

Prevalence of young adult ADHD decreased to 6.3% of the cohort when excluding comorbidities.

Compared with individuals without ADHD, those with childhood ADHD were more likely to be male ($P < .001$), while those with young adult ADHD were more likely to be female ($P < .001$).

Impairment was more common among participants with ADHD, as measured by traffic incidents, criminal behavior, incarceration, suicide attempts and comorbidities.

Approximately 17.2% of children with ADHD continued to have ADHD as young adults and 12.6% of young adults with ADHD had ADHD in childhood.

"Above all, our findings do not support the premise that adulthood ADHD is always a continuation of [childhood ADHD]. Rather, they suggest the existence of two syndromes that have distinct developmental trajectories, with a late onset far more prevalent among adults than a childhood onset. This finding would not mean that ADHD could not be conceptualized as a neurodevelopmental disorder," the researchers wrote. "In both clinical practice and research, it is important to differentiate early- and late-onset disorders, and future investigations should test whether they have different pathophysiologic mechanisms, treatment response, and prognosis. In addition, patients with late-onset adulthood ADHD have clear impairments, and their clinical profile cannot account for only the effect of comorbidities."

"The requirement of a childhood onset has always been a key criterion for the diagnosis of attention-deficit/hyperactivity disorder (ADHD) in adults, but recently this requirement has become surrounded by controversy."

ARTHUR CAYE

– by Amanda Oldt ■

Reference:
Caye A, et al. *JAMA Psychiatry.* 2016;doi:10.1001/jamapsychiatry.2016.0383.

Disclosures: Caye reports no relevant financial disclosures. Please see the full study for a list of all authors' relevant financial disclosures.

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Prescribed stimulant use increases more rapidly among adults vs. youth

From 2010 to 2014, prescribed stimulant use significantly increased among adults, while youth experienced a moderate increase.

"Studies of office-based physician visits by adults showed that the proportion of visits with a prescribed stimulant grew 7-fold, from 0.1% between 1994 and 1997 to 0.7% between 2006 and 2009, and the percentage of visits with ADHD diagnosis doubled from 0.3% between 1999 and 2002 to 0.7% between 2007 and 2010," **Mehmet Burcu, MS,** of University of Maryland, Baltimore, and colleagues wrote. "However, little is known about the trends in stimulant use within the past few years, specifically within commercially insured U.S. populations."

"The increase in adult stimulant use may be largely driven by increases in outpatient diagnoses of adult ADHD."

— MEHMET BURCU, MS

To determine recent trends in stimulant use according to age and sex, researchers applied a repeated cross-sectional design to administrative claims data for 2010 to 2014 among youths aged 0 to 19 years and adults aged 20 to 64 years who were continuously enrolled in a Blue Cross Blue Shield health insurance plan annually in Illinois, New Mexico, Oklahoma or Texas. The study cohort included more than 3.5 million individuals per year.

From 2010 to 2014, stimulant use increased across all age groups, though it was significantly greater among adults ($P < .001$).

Stimulant use increased from 2.7% to 3.1% among children aged 0 to 9 years (adjusted OR = 1.16; 95% CI, 1.13-1.18), from 6.2% to 7.2% in children aged 10 to 19 years (aOR = 1.27; 95% CI, 1.25-1.29); from 2.2% to 3.6% among individuals aged 20 to 39 years (aOR = 1.84; 95% CI, 1.81-1.87); and from 1% to 1.5% among individuals aged 40 to 64 years (aOR = 1.66; 95% CI, 1.63-1.69).

Researchers observed slight but statistically significant differences in increases in stimulant use by sex among participants aged 10 to 19 years and 20 to 39 years.

In 2014, stimulant use was significantly greater among males vs. females aged 0 to 19 years (7.1% vs. 3.5%; $P < .001$), but did not differ by sex among those aged 20 to 34 years (4% vs. 4%; $P = .95$).

Among participants aged 35 to 64 years, stimulant prevalence was greater among women than men (1.9% vs. 1.3%; $P < .001$).

In 2014, amphetamine-related products accounted for the greatest percentage of total stimulant dispensing among adults (83.6%), while methylphenidate-related products were more common among youth (52.5%).

Among individuals prescribed stimulants, clinician-reported ADHD diagnosis was more common among youths than adults (62% vs. 45.5%).

"In a commercially insured population, in just 5 years, between 2010 and 2014, the proportion of adults treated with stimulants grew rapidly in contrast to youths, who had a modest increase in stimulant use," the researchers wrote. "The increase in adult stimulant use may be largely driven by increases in outpatient diagnoses of adult ADHD. However, consistent with previous reports, we show that a large proportion of stimulant-treated adults lacked an ADHD diagnosis, potentially reflecting off-label use. This raises concerns regarding potential nonmedical use of prescription stimulants."

– by Amanda Oldt ■

Reference:
Burcu M, et al. *JAMA Psychiatry.* 2016;doi:10.1001/jamapsychiatry.2016.1182.

Disclosure: The researchers report no relevant financial disclosures.

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Childhood ADHD diagnosis does not always precede adult ADHD

Recent findings showed a significant proportion of individuals with late-onset attention-deficit/hyperactivity disorder did not meet criteria in childhood, suggesting that a lack of a childhood diagnosis should not preclude late-onset diagnosis in adulthood.

"To date, adult attention-deficit/hyperactivity disorder (ADHD) has been conceptualized as a continuation of childhood ADHD. However, recent findings have suggested that, for some individuals, ADHD may not arise until adolescence or adulthood and may be associated with different risk factors and outcomes than childhood ADHD," **Jessica C. Agnew-Blais, ScD,** of King's College London, and colleagues wrote.

To evaluate childhood risk factors and young adult functioning of individuals with persistent, remitted and late-onset adult ADHD, researchers assessed a nationally representative birth cohort from the Environmental Risk Longitudinal Twin Study of 2,232 twins born in England and Wales from 1994 to 1995. Childhood ADHD was evaluated at ages 5, 7, 10 and 12 years. ADHD symptoms and associated impairment, overall functioning and other mental health disorders were examined at age 18 years.

Overall, 247 study participants met diagnostic criteria for childhood ADHD. Of these, 21.9% met criteria for ADHD at age 18 years.

Persistence was associated with more symptoms (OR = 1.11; 95% CI, 1.04-1.19) and lower IQ (OR = 0.98; 95% CI, 0.95-1).

At age 18 years, participants with persistent ADHD had more functional impairment at school or work (OR = 3.3; 95% CI, 2.18-5) and at home or with friends (OR = 6.26; 95% CI, 3.07-12.76), generalized anxiety disorder (OR = 5.19; 95% CI, 2.01-13.38), conduct disorder (OR = 2.03; 95% CI, 1.03-3.99) and marijuana dependence (OR = 2.88; 95% CI, 1.07-7.71), compared with those with remitted ADHD.

Of the 166 participants with adult ADHD, 112 (67.5%) did not meet criteria for ADHD at any childhood assessment.

Logistic regressions analysis indicated participants with late-onset ADHD exhibited fewer externalizing problems (OR = 0.93; 95% CI, 0.91-0.96) and higher IQ (OR = 1.04; 95% CI, 1.02-1.07) in childhood, compared with those with persistent ADHD.

However, ADHD symptoms and impairment and rates of mental health disorders at age 18 years were comparable between participants with late-onset ADHD and those with persistent ADHD.

"Our findings highlight the importance of taking a developmental approach to understanding ADHD. Although many questions remain regarding the nature of late-onset ADHD, this group showed significant levels of ADHD symptoms and impairment, as well as poor functioning and high rates of psychiatric comorbidity. Therefore, the absence of a childhood diagnosis of ADHD should not preclude adults with ADHD from receiving clinical attention," the researchers wrote. "Whether individuals with late-onset vs. childhood-onset ADHD respond differently to treatment is an open question, and further research is required to better understand the causes, course, and optimal treatment of late-onset ADHD." – *by Amanda Oldt* ■

Reference:
Agnew-Blais JC, et al. *JAMA Psychiatry.* 2016;doi:10.1001/jamapsychiatry.2016.0465.

Disclosure: The researchers report no relevant financial disclosures.

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Web intervention on ADHD pediatric care improves quality outcomes

Study findings in Pediatrics showed a web-portal intervention for pediatricians who prescribed medications for children with attention-deficit/hyperactivity disorder improved patients' quality of care and may lead to greater reductions in parent ratings of their children's symptoms.

"Most of these children receive their ADHD care from primary providers. Unfortunately, ADHD care quality in these settings, especially medication monitoring and titration, is often poor."

— JEFFERY N. EPSTEIN, PHD

"Approximately 7% to 9% of elementary school-age children in the U.S. are diagnosed with [ADHD]," **Jeffery N. Epstein, PhD,** professor of pediatrics in behavioral medicine and clinical psychology at Cincinnati Children's Hospital Medical Center, and colleagues wrote. "Most of these children receive their ADHD care from primary providers. Unfortunately, ADHD care quality in these settings, especially medication monitoring and titration, is often poor."

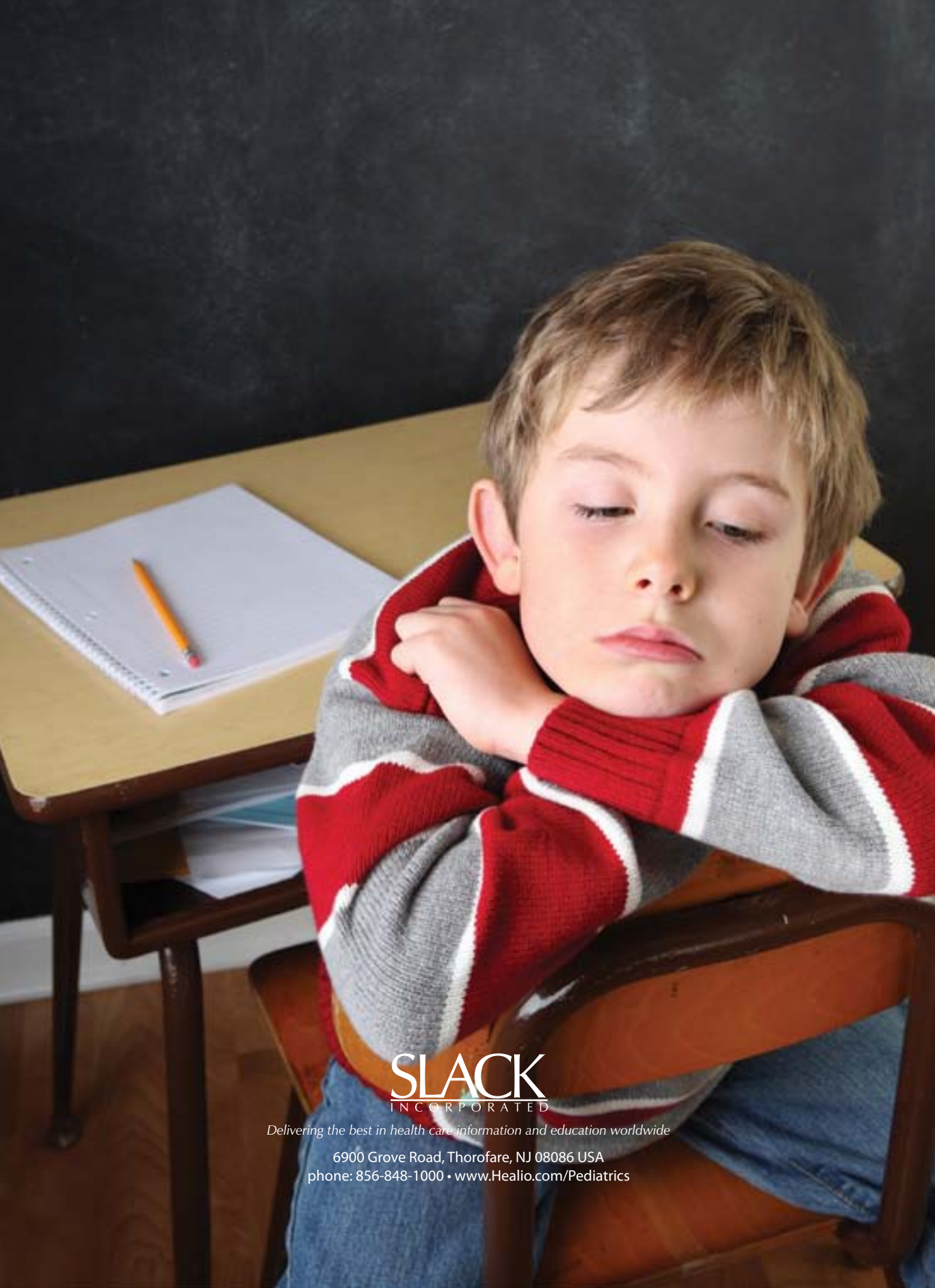
To assess the quality of ADHD community-based care pediatricians provide, Epstein and colleagues examined the effectiveness of a technology-assisted quality improvement (QI) intervention on outcomes among elementary school-aged children with ADHD. The randomized, cluster controlled study included 213 pediatricians at 50 primary care practices who prescribed ADHD medication to children during a 2-year period. Pediatricians were assigned to a technology-assisted QI intervention — including four 1-hour, Web-based training sessions and an ADHD internet portal for monitoring assistance — or a control condition. ADHD treatment methods and parent/teacher rated symptoms were collected from 577 children (36.7% nonwhite) in the first year; 258 were from intervention practices, and 319 were from control practices.

The researchers contacted patients' family members at 3, 6 and 12 months to reassess the parents' judgment on ADHD symptom ratings and contacted teachers at 3 and 6 months after baseline. Among children prescribed ADHD medications (n = 373), pediatricians experienced a significant QI with the web-portal intervention (b = –2.42; *P* = .04), including more treatment contacts and parent/teacher symptom ratings compared with children at control practices. This prompted the researchers to recommend future studies to encourage expanding the software to enable behavioral treatment and implementation to all pediatric ADHD patients.

"Compared with the usual care group, providers in the intervention group had 25% more patient contacts and collected 4.6 and 9.9 times more parent and teacher ratings, respectively," the researchers wrote. "However, even the quality of care achieved at the intervention practices left much room for improvement. For example, providers did not collect parent or teacher ratings during the initial year of ADHD medication treatment for half of their patients." – *by Kate Sherrer* ■

Reference:
Epstein JN, et al. *Pediatrics.* 2016;doi:10.1542/peds.2015-4240.

Disclosures: Epstein reports that he and his institution own the intellectual property and licensing rights to the internet-based software used in this study. He also reports receiving consulting fees and/or travel reimbursement from the AAP. Please see the full study for a list of all other authors' relevant financial disclosures.



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