THE CARLAT REPORT
CHILD PSYCHIATRY

A CME Publication

Subscribe today!
Call 866-348-9279

UNBIASED INFORMATION FOR CHILD PSYCHIATRISTS

Volume 5, Number 6&7
November 2014
Special Double Issue:
worth 2 CME Credits
www.thecarlatchildreport.com

IN THIS ISSUE

ADHD

Learning objectives for this issue:
1. Describe how Vyvanse compares to other stimulants used to treat ADHD. **2.** Detail some of the issues child psychiatrists are likely to face in diagnosing and treating ADHD. **3.** Summarize what is currently known about the use of Intuniv to treat ADHD. **4.** Evaluate some of the current findings in the literature regarding psychiatric treatment.

Vyvanse: A Look at America's Most Prescribed Stimulant

Talia Puzantian, PharmD, BCPP
Clinical Psychopharmacology Consultant in Private Practice, Los Angeles, CA

Dr. Puzantian has disclosed that she has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

Why has Vyvanse become by far the most prescribed stimulant in the United States? Great marketing? A great product? Some combination of the two? And more to the point, should you continue to choose it over its much cheaper competitors? Read on for our take on the Vyvanse phenomenon.

Vyvanse (lisdexamfetamine) was first approved by the US Food and Drug Administration (FDA) for pediatric ADHD in 2007. Later, it was approved for both adults (2008) and adolescents aged 13

Continued on page 2

In Summary

- In 2013, Vyvanse was the eighth most prescribed drug overall in the US, with over 105 million prescriptions and total sales of $1.7 billion
- Its advantages over cheaper competitors are the possibility of lower abuse potential and anecdotal reports of better tolerability
- There have been no adequate studies comparing Vyvanse and other stimulants

Q&A With the Expert

A Balanced Approach to Treating ADHD

Lawrence Diller, MD

Behavioral/Developmental Pediatrician in Private Practice
Assistant Clinical Professor
University of California, San Francisco

Dr. Diller has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CCPR: Dr. Diller, you have published widely on the overdiagnosis and overtreatment of ADHD. Today I want to focus on alternatives to medications for these kids—but first, do you still think that stimulants are being overprescribed in the US?

Dr. Diller: I think stimulants are underprescribed, misprescribed, and overprescribed. There's no question that stimulants work and that they are relatively safe, and I prescribe them often, especially for kids who have severe symptoms—who are at the end of the bell curve. But for the vast majority of children, the issue isn't so much hyperactivity or impulsivity, the issue is a temperament or personality that finds it difficult to do things that they are not interested in—that's how we've come to define ADHD in our country. So yes, my overall sense is that we are overprescribing in the US. We are 4% of the world's population, yet we produce 70% of all stimulants (International Narcotics Control

Continued on page 3

Vyvanse: A Look at America's Most Prescribed Stimulant

Continued from page 1

to 17 (2010). The medication quickly became a go-to medication for prescribers. In 2013, it was the eighth most prescribed drug of any kind in the US, with over 10.5 million prescriptions and total sales of $1.7 billion—far outpacing its closest stimulant competitor, Focalin XR, which came in at number 44 on the list of most prescribed drugs with just over three million scripts.

How it Works

Vyvanse is lisdexamfetamine, which is dextroamphetamine (the molecular name of Dexedrine), bound to a lysine molecule. It remains inactive until hydrolyzing enzymes cleave off the lysine and convert it to the active dextroamphetamine. The manufacturer's claim is that this gives the drug a lower potential for abuse because the active ingredient is only released when the medication is swallowed, making it inactive if snorted or injected. Interestingly, there are numerous web sites instructing would-be amateur chemists on how to perform the hydrolysis reaction at home prior to ingestion in order to have access to the pure dextroamphetamine form (see, for example, http://bit.ly/1yiUFDt).

Vyvanse was approved in each age group based on four-week studies comparing fixed doses of 30, 50, and 70 mg/day to placebo. In addition, a maintenance indication in adults was approved in 2012 by the FDA, based on a placebo-controlled, randomized withdrawal design study of 116 patients who were monitored for relapse symptoms. After randomized drug withdrawal, a majority of patients (75%) given placebo showed symptom relapse by two weeks compared to 9% of those patients who continued on Vyvanse (Brams M et al, *J Clin Psychiatry* 2012;73(7):977–983.)

Similar results were seen in a more recent study with 276 children; 16% of Vyvanse patients had symptom relapse compared to 68% of those on placebo (Coghill DR et al, *J Am Acad Child Adolesc Psychiatry* 2014;53(6):647–657). The fact that stimulant withdrawal leads to renewed symptoms is no shocker, though Shire Pharmaceuticals, which makes Vyvanse, gets kudos for being the first manufacturer to demonstrate this for all age groups.

How it Compares with Other ADHD Medications

So, Vyvanse is better than placebo, both in the short term and long term, but how do we rank it with other ADHD treatments?

All major published clinical trials of the drug have been funded by Shire, and there are no truly robust head-to-head comparator studies with competing stimulants. One crossover study of 6- to 12-year-old children had all 52 subjects start on Adderall XR at 10 mg/day, and doses were individualized to each patient's optimal daily dose over a three-week period. Subjects then entered the double-blind crossover part of the study in which they received all three treatments sequentially (placebo, their optimized Adderall XR dose, an equivalent dose of Vyvanse) and the order of treatments was randomized. Patients improved on each of the stimulant medications when compared to placebo. However, there were not enough subjects to statistically compare the two active treatments, and we cynically wonder if this Shire-funded study was underpowered on purpose, so as to prevent a result that might have made Vyvanse look

Continued on page 3

Vyvanse—In Brief

Generic name	Lisdexamfetamine dimesylate
Manufacturer	Shire Pharmaceuticals
Approval date	February 23, 2007
Approval indications	Acute and maintenance treatment of ADHD for children, adolescents, and adults
Dosages available	20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg capsules
Dosing	Start at 30 mg/day; increase by 10 mg or 20 mg weekly as needed; maximum dose: 70 mg/day
Average cost	About $7/day
Likely marketing points	Decreases the potential for misuse or abuse
Advantages	Possibly lower abuse potential; anecdotal reports of better tolerability
Disadvantages	High cost; company has not adequately compared Vyvanse with other stimulants

EDITORIAL INFORMATION

Publisher: **Daniel Carlat, MD**
CEO: **Steve Zisson**
Executive Editor: **Joanne Finnegan**
Founding Editor: **Caroline Fisher, MD, PhD,** is training director and Chief of Child Psychiatry at Samaritan Health Systems in Corvallis, OR.
Editorial Board:
Jonathan C Gamze, MD, is a psychiatrist in private practice in Arlington Heights, IL.
Georgia Gaveras, DO, is the director of training and education in child and adolescent psychiatry and the director of the child and adolescent psychiatry consultation liaison service at Mount Sinai St. Luke's Hospital in New York, NY.
Ruth Gerson, MD, is a clinical assistant professor of child and adolescent psychiatry and associate director of the Bellevue Hospital Children's Comprehensive psychiatric emergency program in New York, NY.
Peter Parry, MBBS, is consultant child & adolescent psychiatrist and senior lecturer at Flinders University in Adelaide, Australia.
John Preston, PsyD, is a professor emeritus at Alliant International University in Sacramento, CA.
Jess Shatkin, MD, MPH, is vice chair for education at NYU Child Study Center at NYU School of Medicine in New York, NY.
Dorothy Stubbe, MD, is director of residency training and an associate professor of psychiatry at Yale Child Study Center in New Haven, CT.
All editorial content is peer reviewed by the editorial board. Dr. Fisher, Dr. Gamze, Dr. Gaveras, Dr. Gerson, Dr. Parry, Dr. Preston, Dr. Shatkin, and Dr. Stubbe and have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.
This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

Vyvanse: A Look at America's Most Prescribed Stimulant

Continued from page 2

worse than Adderall (Biederman J et al, *Biol Psychiatry* 2007;62(9):970–976).

Another placebo-controlled study of Vyvanse in children, conducted in Europe, included an active reference arm of patients treated with Concerta. A total of 336 subjects were randomized to optimized dosing of Vyvanse (30, 50, or 70 mg/day), Concerta (18, 36, or 54 mg/day), or placebo for seven weeks. At the end of the study, 78% of Vyvanse subjects were deemed responders compared to 61% of Concerta subjects and 14% of placebo subjects. Similar to the Adderall XR study, this study was powered only to compare each of the two active drug groups to placebo, not to each other. Also of note, the maximum dose of Concerta is 54 mg/day in European countries compared to 72 mg/day in the US, which may have explained the lower response rate seen with that group (Coghill D et al, *Eur Neuropsychopharmacol* 2013;23(10):1208–1218).

There is one head-to-head study of Vyvanse compared to the non-stimulant noradrenergic atomoxetine (Strattera) in 267 children with previous inadequate response to methylphenidate (Dittmann RW et al, *CNS Drugs* 2013;27(12):1081–1092). Vyvanse outperformed Strattera, but nobody's falling off their chair with these results, since other studies have established that Strattera is a less effective ADHD treatment than stimulants in general.

Deciding the Merits

Given the absence of well-designed studies comparing Vyvanse with other stimulants, how else are we to decide on its merits? Let's focus on the two other long-acting amphetamine preparations: Dexedrine Spansules and Adderall XR. We can check Dexedrine Spansules off the list, because it is even more expensive than Vyvanse (about $26/day for the brand and about $10/day for the generic). The generic Adderall XR is only $1.50/day, versus Vyvanse at about $7/day.

They both have about the same duration of action (8–12 hours). The long-acting property of Vyvanse is due to its formulation as a prodrug, whereas Adderall XR is a bead-filled capsule that mimics twice daily dosing (50% of beads are immediate-release and 50% are delayed-release). The prodrug design of Vyvanse may decrease the potential for misuse or abuse compared to Adderall XR, which can be snorted or injected. However, there are no studies comparing the abuse liabilities of the two drugs.

Anecdotally, some psychiatrists in the field have told *The Carlat Psychiatry Report (TCPR)* that they prefer Vyvanse because they perceive it as being more tolerable, with a smoother onset and offset of effects than Adderall XR. Are anecdotal impressions worth choosing a drug that's nearly five times the expense of a competitor? You'll be the judge of that one.

By the way, Shire is actively pursuing more indications for Vyvanse. Though they recently halted its development as a treatment for depression after two failed late-stage clinical trials, they continue to seek approval for its use in binge eating disorder and plan studies for ADHD in the very young (4- to 5-year-olds).

DR. CARLAT'S VERDICT: Vyvanse: Maybe a little less addictive, maybe a little more tolerable…but certainly much more expensive than Adderall XR and Concerta. We give Shire an A+ for marketing.

Expert Interview

Continued from page 1

Board report, http://bit.ly/1iOCX6z). In 2013, 194 tons of legal stimulants were produced in the US (see Aggregate Production Quota History for Selected Substances, http://1.usa.gov/1sg2LJw). In addition, according to a telephone survey by the US Centers for Disease Control and Prevention (CDC), 10% of all parents have been told by someone that their child has ADHD (Visser SN et al, *J Am Acad Child Adolesc Psychiatry* 2014;53(1):34–46). In certain states, such as North Carolina, that figure goes up to 30% of parents who have been told their son has ADHD.

CCPR: How do these figures compare to the actual prevalence of ADHD?

Dr. Diller: That's hard to say, because the diagnosis is subjective. The ability to self-regulate falls in a bell-shaped curve. Where you draw the line between variations in "normal temperament" and a "disorder" will vary depending on who's doing the evaluating. But the vast majority of kids with ADHD have the mild to moderate variety. And these are kids who deserve a trial of non-pharmacologic interventions first.

CCPR: So how do you approach your comprehensive evaluation?

Dr. Diller: First, I'll let parents know that I won't necessarily be prescribing any medications immediately, and give them a little background on how there is an overreliance on medications for ADHD because in our culture there is pressure on parents, teachers, and children to perform. They appreciate that. Many families who come to me, see that I am an MD and they expect medications, and when they hear a doctor talking about non-drug interventions, 95% of the parents are very pleased to be given that option.

CCPR: Do you start your evaluation by talking to the family or the patient, or both?

Dr. Diller: The first session is a meeting with the parents, and I can't overemphasize the importance of involving both parents. Even in divided households with a non-custodial parent, who is often the father, including that parent is critical. Even if he only sees the kid every other weekend, my experience is that an uninvolved father, who disagrees with a behavioral or a medication

Continued on page 4

Expert Interview
Continued from page 3

plan, can undo in a weekend what the mother and I have set up over a three-month period.

CCPR: And after that first meeting, do you meet with the patient?

Dr. Diller: Usually I'll first meet with the patient during the second session, which will be a conjoint family meeting. Everybody who lives in the household is invited, including the parents, the patient, the siblings, the grandparents, etc. I find that this is the single most valuable 45 minutes I spend with the child, because I can see the child's behavior within the primary social system.

CCPR: Why is that so valuable?

Dr. Diller: I'll give you an example. One scenario in a conjoint meeting is that the identified patient sits reasonably well in the office but his younger sibling is out of control, and the parents are ineffectually trying to deal with that sibling—this gives me a great deal of insight into the family system. For one thing, I know that the parents are having to deal with a lot of stuff besides the patient. You just can't get that insight through regular history taking.

CCPR: And how do you structure the conjoint family session?

Dr. Diller: We start out doing a little talking where I have the parents ask the children why they think they've come to see the doctor. I have some toys in my office and I'll generally allow a brief time for family play. I always assign the family a drawing game. The instructions are, "Here are some markers and paper. I'd like you to do something together with the markers and paper for five minutes, but there's no talking." This turns out to be a very revealing five minutes. For example, a common scenario is that the parents hesitate, and the children start drawing their own pictures, even though I said, "Do something together." The parents then start to draw on their own, but then mom tries to join Johnny's (the patient) picture, but he hits her hand and she backs away. What has happened very quickly in the office is that the children have created the rule system in the family, and Johnny experiences mom's efforts to be involved as a violation of his territory. I ask them if they've experienced this dynamic outside of the drawing game, in which there's a power void that is filled with the child. I explain that in life, 90% of what kids do requires that they comply with someone's rules, and that if you leave it up to kids to establish these rules, there are going to be some negative consequences. This is a prelude to working with the parents on basic parenting skills, such as providing immediate consequences and time outs when needed.

CCPR: Do you also have an individual session with the patient?

Dr. Diller: Yes, that's usually the third session. I start by asking a few questions, engaging with him, which gives me a sense of what his social abilities are and whether he can stick with me on a subject. Then, for kids under 12, I give them 10 or 15 minutes to play, which is usually going to the sand tray in my office, and using toys to create a story. The majority of kids who aren't on the extreme of hyperactivity do fine in this task. But the kid who is really struggling is overwhelmed by the number of choices, and might put toys randomly into the sand, and then change them abruptly, with little organization. After that, if the child has not already had a recent educational evaluation by the school, I'll spend 20 to 30 minutes and go through some graded reading paragraphs, a math test, and a screen for auditory processing. I do this not to document a learning disability, but because this will give me a clue if there is a significant learning problem. A kid might look fine during play but once I give him a pencil, he starts showing symptoms, rocking, and yawning, or feel overwhelmed by some simple processing tasks. If I see some obvious learning issues, I make sure to have the parents initiate an educational evaluation through the school.

CCPR: It really sounds like you're providing a one-stop shop for these families.

Dr. Diller: Yes, certainly other providers could do some of these things, but the key issue is whether the MD wants to do or know anything else besides deciding on medicine. There are economic issues that drive the MD in how he or she maintains the practice, because you can make twice as much money doing four med checks as you can spending 45 or 50 minutes with the family or the kid.

CCPR: So overall, your typical evaluation requires three sessions?

Dr. Diller: Yes, three billable sessions, because you can't really make the diagnosis in 15 minutes. I do one other thing which is important, and that is I talk to the teacher on the phone rather than rely on a form. Many clinicians will have the teacher fill out a Vanderbilt Assessment Scale, which is certainly better than nothing, but I find that it's much more valuable to actually get the teacher on the phone. The problem is that this is not billable through insurance. The way I handle it is, I don't charge unless the conversation lasts longer than 15 minutes, and then I'll bill the parents for my time.

CCPR: Why is actually talking to the teacher so important? What do you find out?

Dr. Diller: Talking is important because the teacher questionnaires only ask about negative behaviors—does the child fidget, blurt out things, etc. When I talk to teachers, I ask in an open-ended way, "Tell me about this child in your classroom in terms of both strengths and weaknesses." I find that many teachers are trained these days to describe every type of misbehavior in the language of ADHD, especially using the word "focus"—as in, "He doesn't focus in the classroom." If so, I tell the teachers, "Not focusing is an *interpretation* of behavior, but can you tell me what he's doing or not doing that's the problem." Because there are multiple reasons why children don't do what they are supposed to do.

CCPR: So once you are done with this evaluation, what's the next step?

Dr. Diller: In the fourth visit, I sit down with parents and go over the findings. I lay out what I feel I can do for them. I make sure

Continued on page 5

Expert Interview
Continued from page 4

they know that I'm not talking about weekly visits over the next year, but maybe three or four visits over the next two months, and that primarily I'll be working with the parents.

CCPR: Do you ever start medications right away?

Dr. Diller: For a small percentage of kids, about one-eighth of my practice, I find that they are so hyperactive that they need to be on medications immediately before we can do anything else. But the vast majority of kids get a trial period of from two to three months where behavioral and educational interventions are tried. Of this group, about 50% will end up on meds, eventually, but 50% will be fine without medicines.

"I think stimulants are underprescribed, misprescribed, and overprescribed."

Lawrence Diller, MD

CCPR: What are the specific behavioral interventions that you usually recommend?

Dr. Diller: My first point is usually to address the common misconception that the child is incapable of doing certain things because of ADHD. I'll say, "You should throw out the idea that Johnny *can't* do this or that, because based on my experience, certain things are just *harder* for him to do, and require specific strategies." The key behavioral strategy is immediately linking demands and consequences, and this leads right to my main recommendation, which is a parenting skills intervention based on the book "*1-2-3 Magic*" (Phelan TW. Glen Ellyn, IL: Parentmagic Inc.; 2014). This is a deceptively simple technique, in which parents count kids to three and then give them a time out if the behavior continues. I'll often introduce this by saying to parents, "You know when Johnny hit his sister and he immediately looked at you to see your reaction? That's called a test." I ask if they agree, and they usually say "yes." Then I say, "Why do children test their parents? They test boundaries to develop consistent responses because it makes them feel more secure." A child has huge anxiety when he thinks, "I'm too little to take care of myself but I'm stronger than my parents." Most parents understand that this is a reasonable justification for enforcing limits.

CCPR: What's so magical about *1-2-3 Magic*?

Dr. Diller: Parents only need to explain it to the kid one time, and that's it. Sometimes while they are explaining it, the kid starts mouthing off, and the parents say, "That's ONE." I tell the parents that for the first 72 hours it will be horrible torture as you make the shift from being powerless to having consistent power. But I'll say, "If you stick with this plan, I guarantee (I'll sound like a car salesman) improvement in 72 hours. If you don't see improvement in 72 hours, then you are to call me, even on the weekend, because you must be doing something wrong." The magic is that after the kids have been sent to time out once or twice, the parent says "ONE" and the kid freezes like a lightning bolt has hit him. The other part of the magic is that over a period of a couple of weeks, especially with the younger kids, it looks like they are on Ritalin, because the behavioral change can be quite profound. However, for some of the parents, it's not a natural way of acting. Down the line, for these families the "magic" compliance wears away as they do what is natural to them.

CCPR: Are there other behavioral interventions?

Dr. Diller: The other intervention is to make sure the parents go to the school and get a basic educational evaluation rolling. An SST (Student Study Team) evaluation has to be completed within two weeks, whereas an Individualized Education Plan (IEP) evaluation, which is much broader, can take up to 120 days. I also recommend a school-based behavioral intervention, appropriate mainly for children fifth grade and younger, which is called the daily report card. This is just a piece of paper on the kid's desk, and when he completes a task without any or only one reminder, then the teacher puts a dollar sign or a sticker in one of the boxes immediately upon completion. I tell the kids, "This is an opportunity for you to win fabulous cash prizes and trips to the Bahamas." The stickers equal computer time, or trips to the ice cream store, or his choice of a DVD at the end of the week if he gets enough of them. It's even better if the teachers have lottery boxes or treasure chests at the end of the week—you wouldn't believe what the kids are willing to do get an extra ticket to put into the lottery box.

CCPR: After your evaluation, as you follow the family, are there any tips that help the parents be successful in their behavioral interventions?

Dr. Diller: I use the "swordfish" technique. This helps parents support one another in effectively using *1-2-3 Magic*. If one parent is trying to engage the child in setting limits, but is not doing well, the observer parent says "swordfish" to remind the disciplining parent to get back on track. "Swordfish" is from the Marx Brothers' *Horse Feathers* movie. It's the password Groucho uses with Chiko to get into the speakeasy.

CCPR: I like the thoroughness of your evaluation process. But there are certainly some doctors who are either unable or unwilling to budget their time this way. If we did want to farm out some of these aspects of the evaluation, how do you recommend that we find someone who works well with parents and the schools in this way?

Dr. Diller: Unfortunately, it's hard to find. In my middle/upper middle class community, I can think of only two or three therapists who will do a conjoint family interview or talk to the teacher. Most therapists do individual work with kids, which often will not lead to much improvement in ADHD symptoms. In fact, in my practice a typical pattern is for parents to send their kids to therapy for six to 12 months, see no change, and then to come to me. Sadly, child psychiatrists in my area are typically not doing conjoint family interviews, because the field has moved to a medication model.

CCPR: Thank you, Dr. Diller.

Intuniv: Exorbitant, Sedating, and Second-Line

Talia Puzantian, PharmD, BCPP
Clinical Psychopharmacology Consultant in Private Practice
Los Angeles, CA

Dr. Puzantian has disclosed that she has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

Guanfacine, a drug originally used to treat hypertension, has been reformulated and now has new life as a medication to treat ADHD in children.

An alpha-2A agonist, this medication was initially marketed as Tenex (now available as a generic) for treating hypertension. However, centrally-acting antihypertensives such as guanfacine fell out of favor as newer and less sedating antihypertensives came on the scene.

In more recent years, guanfacine use has had a resurgence, but this time in children with ADHD. Small pilot studies conducted as far back as 20 years ago showed it had promise in this group. And, in 2009, an extended-release formulation of guanfacine (GXR) marketed as Intuniv, was approved by the US Food and Drug Administration (FDA) for 6 to 17 year olds with ADHD, either as monotherapy or as an adjunct to stimulants. Just to clarify, guanfacine immediate-release is available as a generic, but GRX is available as brand-name Intuniv only.

What Studies Show

The FDA approval was based on results from two controlled clinical trials comparing GXR (1 mg to 4 mg/day) to placebo in a total of 669 children and adolescents. GXR was significantly more effective for inattentive and hyperactive-impulsive symptoms than placebo at all doses. But, when the data for adolescents aged 13 to 17 years were separated, no significant difference was noted in that group. A third preclinical study assessed the efficacy of adjunctive GXR in 461 children with suboptimal response to stimulants. Significant improvement was seen in all GXR groups (1 mg to 4 mg/day) over placebo groups, this time including the adolescents.

Unfortunately, there have been no published trials comparing guanfacine to other approved medications for ADHD although a search of clinical trial registries finds two unpublished head-to-head studies, one versus methylphenidate (NCT00429273) and the other versus atomoxetine (NCT01244490). Until we can see results of those studies, the best we can do to determine guanfacine's place in therapy is to take a look at effect sizes. Effect size is a measure that describes the magnitude of treatment effect. Studies of GXR have shown effect sizes between 0.43 and 0.86, depending on dose used. This is a lower effect size than those reported for stimulants (0.8 to 1.2) and about the same as for atomoxetine (0.59 to 0.64). By comparison, GXR used as an adjunct to stimulants resulted in a lower effect size (about 0.4).

Two studies examined the use of guanfacine in ADHD patients with comorbidities. One controlled trial showed significant improvement, compared to placebo, in reducing tic severity and another showed significant improvement in oppositional symptoms. This isn't really enough to make a hearty statement but it would be nice to see if more studies would help determine which types of patients may be the best candidates for guanfacine therapy.

A marked difference between guanfacine and stimulants are the side effects. Stimulants commonly cause insomnia, anorexia, and tachycardia. The most common side effects of guanfacine were fatigue and somnolence, which were reported by as many as 33% to 44% of patients. Up to 18% of patients discontinued treatment because of these effects. Although sedation was very common and dose-related in the monotherapy trials, it occurred less frequently when guanfacine was used as an adjunct to stimulant. Patients also reported headache, nausea, and dry mouth with guanfacine but these tended to be mild to moderate. Dose-related decreases in blood pressure can occur rarely and warrant caution particularly when treatment is initiated or when dose is increased.

Price and Pharmacokinetics

The majority of the controlled trial data with guanfacine in ADHD is with the brand name only GXR (Intuniv). The older, immediate-release guanfacine is available, in identical strengths, for a much cheaper price—about $0.80 per tablet versus over $8 per tablet for Intuniv. Seems like a no-brainer to substitute the generic, right? Well, the manufacturer of Intuniv warns against substituting the cheaper, generic, immediate-release guanfacine for its product. The company bases this on the differing pharmacokinetic properties. From data in adults, the extended-release formulation of guanfacine is reported to have a peak serum level that is about 60% lower and occurs three hours later than that with immediate-release. This is not an unusual pharmacokinetic difference when comparing an extended-release to an immediate-release formulation and, oftentimes, this relates to lower rates of adverse effects seen with an extended-release formulation. Interestingly, rates of somnolence in patients taking GXR as monotherapy compared to patients taking immediate-release guanfacine appear similar when comparing reported frequencies in the package inserts (not head-to-head studies unfortunately, but the best we have for comparison).

The pharmacokinetics do suggest that substituting on a mg-to-mg basis is not recommended but an adjusted dosing substitution would be appropriate. The dosing recommendation for Intuniv is to start at 1 mg/day and to increase by 1 mg/day weekly to a maximum of 4 mg/day. The immediate-release generic can be initiated at 0.5–1 mg QHS (at bedtime) and increased by 1 mg/day weekly to a maximum of 2 mg to 4 mg/day, depending on the patient's weight (60–90 pounds: 2 mg/day; 90–99 pounds: 3 mg/day; >99 pounds: 4 mg/day).

The dose of immediate-release formulation is usually divided to minimize hypotension or orthostasis, which occur only rarely. It's interesting to note that the half-lives of the two formulations do not differ by much, unlike other medications with extended-release formulations. In adults, Intuniv has a half-life (t ½) of 18 hours while immediate-release has a half-life (t ½) of 16 hours (it's about 13–14 hours in children).

Continued on page 8

Research Updates IN PSYCHIATRY

ANXIETY

Pet Therapy for College Students

College can be a time of stress and loneliness for students. A new study shows that pet therapy may help ease the suffering.

In a pilot study aimed at assessing the effectiveness of an animal-assisted therapy (AAT) outreach program, researchers invited 55 undergraduate students at a small liberal arts college in the Southeast to participate. The students interacted with one of the college's counseling staff, who is a registered Pet Partners therapy team member, and her therapy dog.

The sessions took place in a group setting at a residence hall lobby on the college campus twice a month for an academic quarter. Students were invited to drop-in and interact with the dog, the counselor, and other attendees for a period of two hours. The average attendance at each event was 10 to 15 students and participants spent anywhere from five minutes to two hours with the dog. Students were able to pet, hug, feed, brush, draw, photograph, sit near, and play fetch with the dog. The counselor provided information about the college's counseling center, but did not provide counseling services or psychoeducation during the sessions.

The researchers found the program reduced symptoms of anxiety and loneliness in the students by 60%. Students (84%) said interaction with the dog was the most impactful aspect of the intervention. The other 16% said interaction with other students and staff members was most helpful. There was no comparator treatment, and certainly a double blind study would have been hard to pull off—maybe they could have used stuffed animals? Nonetheless, this intervention is easy to implement and inexpensive, and is probably worth trying. In fact, AAT outreach is gaining momentum on college campuses nationwide (Stewart LA et al, *J Creativ Ment Health* 2014;9(3):332–345).

CCPR's Take: Pet a dog, feel better.

AUTISM

Danish Study Explains Most of Autism's Rise

It's now estimated that about one in 68 children in the US have been diagnosed with autism spectrum disorder (ASD), a 123% increase since 2002, when a monitoring network funded by the US Centers for Disease Control and Prevention (CDC) began its reporting.

There is disagreement about the causes of this increased incidence of autism. Debate has focused on whether the rise in cases is an artifact caused by increased diagnosis and reporting, or if there is some unknown pathogenic factor in the environment that is causing an actual increase in new cases. A new study out of Denmark provides support for the artifact argument.

Researchers analyzed information from nearly 678,000 children born in Denmark from 1980 to 1991, who were followed until 2011. Of those children, 3,956 were diagnosed with autism, with a sharp increase after 1994. Researchers found that there were only 192 diagnoses reported from 1980 to 1993; 100 from 1994 to 1995; and an astonishing 3,665 (95% of the total) were reported from 1996 to 2011.

What happened in 1994? That was when the *ICD-10* was introduced, in which the criteria for diagnosis were changed in ways that made it easier to diagnose. These changes included recognizing autism as a spectrum of disorders (rather than as a subgroup of schizophrenia in *ICD-8*, which was the previous version used in Denmark) and various changes in the diagnostic criteria. Then, in 1995, a change in reporting practices occurred. Previously, autism could be diagnosed only in inpatient settings; after 1995, outpatient diagnoses were allowed.

Using statistical techniques that predicted changes in diagnostic rates based on past trends, the researchers estimated that about 60% of the increase in autism prevalence in Denmark can be explained by changes in diagnostic criteria and in reporting practices. This means that 40% of the increase remained unexplained. Researchers suggested that generally growing awareness about autism might contribute, but that further studies are needed to explain those changes (Hansen SN et al, *JAMA Pediatr* 2014; Epub ahead of print).

CCPR's Take: Here's another piece of evidence arguing that the apparent epidemic in autism is just that: apparent.

DEPRESSION

To Prevent Depression in Teens, Teach about Change

Transitioning to high school can be a tough time, and studies have shown that teenagers are increasingly likely to have symptoms of depression over the course of their freshman year of school. Now an intriguing study seems to show that a simple intervention can ease these symptoms quite effectively.

Researchers recruited 599 ninth-grade freshman students from three different high schools in northern California. The students were randomly assigned to participate in one of two classroom exercises during the first few weeks of school. In one group, 379 students were taught the "incremental" theory of personality, which holds that individuals have the potential to change. The students took part in a brief self-administered reading and writing activity intended to convey two messages: a) if you are excluded or victimized, it is not due to a fixed, personal deficiency on your part and b) people who exclude or victimize you are not fixed, bad people, but instead have complicated motivations that are also subject to change. In other words, people's personalities can change and social adversities need not be permanent.

Conditions for the control group were the same, except those students learned about the malleability of athletic abilities, not personality theory.

Continued on page 8

Research Updates

Continued from page 7

When students were asked to self-report depressive symptoms nine months later, at the end of the school year, the students assigned to the intervention group showed no increase in symptoms, whereas those in the control group showed a 39% increase in negative mood, feelings of ineffectiveness, and low esteem. Thus, although the intervention did not actually treat depression, it slowed the normal increase in depressive symptoms during that first year of high school (Miu SE and Yeager DS, *Clinical Psychological Science* 2014;published online).

CCPR's Take: While the intervention tested here was a didactic exercise taught to many students at once, you can teach the same basic messages to individual teens in the office, and it may help them gain a perspective that can ward off future depressive symptoms.

SUBSTANCE ABUSE

Daily Marijuana Use by Teens Creates Life Problems

A new study provides strong evidence that chronic marijuana use during adolescence can lead to significant social and psychiatric issues later in life.

Researchers performed a meta-analysis of three longitudinal studies (conduced in Australia or New Zealand) that measured the association of marijuana use with a variety of potential negative outcomes. The studies measured frequency of use before 17 years of age (never, less than monthly, monthly or more, weekly or more, or daily). The number of participants varied depending on the outcome being measured from 2,537 to 3,765 teens.

Seven potential outcomes were measured: completion of high school, receiving a university degree, dependence on marijuana, use of other illicit drugs, suicide attempts, development of depression, and dependence on welfare. The study by researchers in Australia and New Zealand found that teens who use marijuana daily before age 17 are 63% less likely to get a high school diploma than those who never used cannabis and are 18 times more likely to become dependent on the drug. In the United States, about 7% of high school seniors are daily or near-daily marijuana users, according to a 2013 survey.

There were clear and statistically significant associations between frequency of use and five of the adverse outcomes. Those who were daily users before age 17 were less likely than non-users to complete high school or to attain a university degree, and far more likely to become dependent on cannabis, use other illicit drugs, and attempt suicide.

These associations do not necessarily prove causality, because it's possible that unidentified factors may lead to these negative outcomes. Nonetheless, the researchers controlled for many possible confounding factors, and found a dose response relationship (the heavier the marijuana use, the stronger the associations).

Given the growing movement to decriminalize or legalize marijuana use in several US states, as well as some Latin American countries, the researchers said those efforts should be carefully assessed to ensure they don't increase adolescent marijuana use and the potentially adverse effects (Silins E et al, *Lancet Psychiatry* 2014:1(4):286–293).

CCPR's Take: While not definitive, this is the most compelling evidence yet that daily pot smoking is bad for teens in the long-term.

❖ ❖ ❖

Intuniv: Exorbitant, Sedating, and Second-Line

Continued from page 6

DR. CARLAT'S VERDICT: Is Intuniv something new? Yes, this is something new for ADHD; it's not simply another stimulant with the standard potential problems of substance abuse, insomnia, and poor appetite. It's a sedating agent that could be beneficial for some patients. It seems to be less effective overall than stimulants. But, for certain types of children, particularly younger children or those with certain comorbidities, it may be a decent second-line option or an add-on to stimulants. The tenfold difference in price between the extended-release and immediate-release products is extremely difficult to justify, so go with the cheaper, generic, immediate-release first.

Intuniv—In Brief

Generic name	Guanfacine extended-release tablets (GXR)
Manufacturer	Shire Pharmaceuticals
Approval date	September 2, 2009
Approval indications	ADHD as monotherapy and as adjunctive therapy to stimulant medications for children and adolescents (6 to 17 years)
Dosages available	1 mg, 2 mg, 3 mg, and 4 mg
Dosing	1 mg to 4 mg once daily, morning or evening; begin at 1 mg/day and adjust in increments of no more than 1 mg/week
Average cost	Over $8 per tablet
Likely marketing points	Fewer side effects; in cases with comorbidities, may reduce tic severity and improve oppositional symptoms
Advantages vs stimulants	Less jitteriness and insomnia; no abuse potential
Disadvantages vs stimulants	Can be sedating; delayed onset of effect and lower efficacy rate vs stimulants; very expensive in branded form

News of Note

FDA Notice: Be Wary of Some Generic Versions of Concerta

Whether generics are really therapeutically equivalent to branded versions of drugs has long been controversial. The US Food and Drug Administration (FDA) requires that generic companies demonstrate "bioequivalence" before they can be marketed, although these studies are conducted with healthy volunteers. Nonetheless, most of our patients are taking generics, and we hardly ever hear complaints.

Rarely, the FDA itself flags problems with generics—as they recently did regarding two generic versions of Concerta (methylphenidate extended-release) (http://1.usa.gov/11VqUyF). The FDA's action came after it re-examined previously submitted data for the three generic versions of Concerta currently on the market. They found that the generic versions manufactured by Mallinckrodt Pharmaceuticals and Kudco Ireland delivered methylphenidate (MPH) at a slower rate over 10 to 12 hours than branded Concerta. Only Janssen Pharmaceutical's generic version (marketed as Actavis) released MPH at the same rate.

The FDA's action included downgrading the therapeutic equivalence (TE) rating for the Mallinckrodt and Kudco products from AB to BX. That means these two generics are still approved for use and can be prescribed, but are no longer recommended as automatic substitutes for Concerta.

What this means for prescribers depends on the scenario. Scenario A: Your patient is on one of the slow versions of Concerta and is doing perfectly well—no change needed. Scenario B: Your patient is on a slow generic and isn't doing well—switch to Concerta or Activis. Scenario C: You are newly starting a patient on Concerta, or switching from brand to generic—specify on your script that you want it to be filled with Activis.

By the way, the FDA told Mallinckrodt and Kudco Ireland in November to fix their products within six months or to voluntarily withdraw them from the market. We'll keep you apprised.

Omega Fatty Acids Might Help Kids with Attention Deficits

Given new research from Sweden, it won't hurt—and might help—for clinicians to suggest their patients with attention deficit disorder (ADD) take supplements of the fatty acids omega 3 and 6.

The supplements can help children and adolescents with ADD, which is the inattentive subtype of attention-deficit hyperactivity disorder (ADHD), according to the findings of a dissertation done at the Sahlgrenska Academy at the University of Gothenburg.

In a double-blind study, researchers gave 75 children diagnosed with ADHD either omega 3 and 6 or a placebo over three months. Then they gave all the participants the fatty acid supplements over the next three months. While there was no major improvement for the group as a whole, the researchers found in 35% of the participants who had ADD, there was an improvement in symptoms, including being attentive for more than short periods of time. Blood samples also showed those children with an improvement had a better balance between the two fatty acids.

The research also found that a cognitive training program, called Collaborative Problem Solving (CPS), can improve problem behavior in children with ADHD, according to a university news release (http://bit.ly/1pKwWwN). It can be a good alternative or complement in the treatment of ADHD, as well as oppositional defiant disorder (ODD), researchers found. The study included 17 children, who along with their family members, received up to 10 weeks of help in training cognitive ability and solving problematic situations. The families were then asked how much the child's behavior problems improved immediately after treatment, as well as six months later. Half reported a large or very large improvement.

Those who still experienced severe ADHD symptoms at completion of the CPS training were given the chance to supplement treatment with stimulant medications. In a six month follow-up, 81% of all the participating families experienced a large or very large improvement, according to the university news release. Go to http://hdl.handle.net/2077/36752 to read the dissertation.

Pediatrician Policy Statement: Schools Should Start Later for Healthier Teens

School districts should move start times for middle and high schools to 8:30 a.m. or later, so that students can get at least 8.5 hours of sleep per night, according to the American Academy of Pediatrics.

In a policy statement published in August in *Pediatrics*, the organization that represents the nation's pediatricians said later school start times would benefit adolescents' health, safety, and academic performance. The evidence strongly implicates early school start times as a contributor to insufficient sleep in these teens, who need an optimum 8.5 to 9.5 hours of sleep each night (Adolescent Sleep Working Group; Committee on Adolescence; Council on School Health; *Pediatrics* 2014;134(3):642–649).

A National Sleep Foundation poll found 87% of high school students in the US were getting less than the recommended amount of sleep on school nights, with high school seniors averaging less than seven hours. Studies have found that a lack of sleep in teens increases the risk of traffic accidents and makes them more vulnerable to depression and obesity. Teens who get more sleep also do better academically.

It's not just a question of kids getting to bed early. Biology

Continued on page 10

News of Note
Continued from page 9

plays a role, so the average teen has difficulty falling asleep before 11 p.m., according to the policy statement. Napping, trying to catch up on sleep on the weekends, and caffeine consumption can temporarily counteract sleepiness, but aren't a substitute for regular, sufficient sleep. Physicians should make adolescents aware of the need for optimal sleep and encourage parents to get involved in setting bedtimes and supervising activities such as social networking and electronic media use in their kids' bedrooms, the group said.

CDC Study: Kids Are Flocking to e-Cigarettes

More than a quarter-million middle school and high school students who had never smoked regular cigarettes used e-cigarettes in 2013, according to a study released by the US Centers for Disease Control and Prevention (CDC) (http://1.usa.gov/1p5Cr1v). And lots more kids—three times as many as in 2011—have used e-cigarettes.

The CDC study, published in the journal *Nicotine and Tobacco Research,* reported about 79,000 students used e-cigarettes in 2011, a number that increased to more than 263,000 in 2013. The data was from the 2011, 2012, and 2013 National Youth Tobacco surveys of middle and high school students. The survey asked respondents whether they had intentions to smoke regular cigarettes. Those who used e-cigarettes were more likely to indicate they have intentions to try smoking tobacco within the next year (43.9%) compared to those who never used e-cigarettes (21.5%).

The Sunshine Act is Out: Now the World Can See What Drug Companies are Paying You

Intended to create financial transparency when it comes to payments from drug manufacturers to physicians, the Centers for Medicare & Medicaid Services (CMS) released reports on Sunshine Act data for 2013 to the public September 30. You can find the reports at http://cms.gov/openpayments.

The reports are the long-awaited result of the Physician Payments Sunshine Act, which requires manufacturers of drugs, medical devices, and biologicals that participate in US federal healthcare programs to report certain payments given to physicians and teaching hospitals. CMS, charged with implementing the legislation, has called it the Open Payments Program.

Physicians are advised to check the site and know what is reported about them. By completing a three-step registration process with CMS, physicians can review their data to make sure it is accurate. You can read commentary about the Sunshine Act and the new program from our publisher Daniel Carlat, MD, on the Carlat Psychiatry Blog at http://carlatpsychiatry.blogspot.com.

Following Release from Prison, Suicide Risk Eighteen Times Higher

Many states are looking for ways to relieve overcrowding in their prisons and jails. For instance, the state of California just passed Proposition 47, which reduces penalties for drug possession and other nonviolent crimes. California is the first state in the nation to downgrade nonviolent and drug-related cases from felonies to misdemeanors. The result is that thousands of felons are now eligible for immediate release from prisons and jails.

A new study, however, reveals that people who have been in prison run a higher risk of committing suicide, particularly just after their release. The risk is 18 times higher than in the general population, according to a study done by researchers from Karolinska Institutet in Sweden (Haglund A et al, *J Clin Psychiatry* 2014:75(10):1047–1053). By far, the greatest risk of suicide comes in the first few months after release (with the incidence rate highest during the first 28 days). Risk is increased among individuals with a previous psychiatric disorder, a history of substance abuse, and previous suicide attempts.

While the study looked at prisoners released from Swedish prisons, researchers said the findings are consistent with those from other developed nations such as the US. They said facilitating transition to life outside prison, as well as clinical monitoring during the first few months after release, may be needed to prevent suicide (http://bit.ly/1uZ1sV8).

Debate Rages On Over 'Black Box' Warning on Antidepressants

It's been 10 years since the US Food and Drug Administration (FDA) put a so-called 'black box' warning on certain antidepressants because of fears they can cause suicidal thoughts and behavior.

The psychiatric community continues to debate the value of that warning, and a pair of opposing viewpoints was recently featured in the *New England Journal of Medicine*. One called for removal of the warnings (http://bit.ly/1EC0cJb), while the other, written by a medical reviewer at the FDA and proponent of broader antidepressant labeling, challenged the safety claims of the anti-black box crowd (http://bit.ly/1olxGr1).

Continued on page 12

CME Post-Test

CME Notice: The test below is intended to be for **practice only.** All subscribers must take their tests online at www.thecarlatchildreport.com. If you cannot take your test online, please call 866-348-9279 or email info@thecarlatreport.com.

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatChildReport.com to take the post-test. You must answer at least six questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by November 30, 2015. As a subscriber to *CCPR,* you already have a username and password to log on www.TheCarlatChildReport.com. To obtain your username and password, please email info@thecarlatreport.com or call 978-499-0583.

The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Carlat CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Carlat CME Institute maintains responsibility for this program and its content. Carlat CME Institute designates this enduring material educational activity for a maximum of two (2) *AMA PRA Category 1 Credit*™ or 2 CE for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

Below are the questions for this month's CME post test. This page is intended as a study guide. Please complete the test online at www.TheCarlatChildReport.com. Note: Learning objectives are listed on page 1.

1. Shire Pharmaceuticals has marketed the drug Vyvanse as having what advantage over other competing stimulants (Learning Objective #1)?

   [ ] a) It is less expensive than competitors
   [ ] b) It has a decreased potential for misuse or abuse
   [ ] c) It has a longer duration of action
   [ ] d) It has no side effects

2. Lawrence Diller, MD, begins his evaluation of a child suspected of having ADHD with which of the following steps (LO #2)?

   [ ] a) An interview with the child
   [ ] b) An interview with the custodial parent only
   [ ] c) An interview with both parents
   [ ] d) An interview with the child's teacher

3. Of the children with ADHD where Dr. Diller first tries behavioral and educational interventions for two to three months, roughly what percentage eventually are placed on medications (LO #2)?

   [ ] a) 10% [ ] b) 25% [ ] c) 50% [ ] d) 75%

4. Intuniv differs from the original formulation of guanfacine that was used to treat hypertension in that it is an extended-release formula (LO #3).

   [ ] a) True [ ] b) False

5. A study by researchers in Australia and New Zealand found which of the following was true for teens who use marijuana daily before the age of 17 (LO #4)?

   [ ] a) They are less likely to use other drugs than those who never used marijuana
   [ ] b) They are less likely to get a high school diploma
   [ ] c) They are less likely to become dependent on marijuana
   [ ] d) They are less likely to attempt suicide

6. A study of an animal-assisted therapy outreach program for college students found which of the following was true (LO #4)?

   [ ] a) Students said interaction with other students was the most helpful aspect of the intervention
   [ ] b) While students said playing with the dog was fun, it had no impact on tests measuring anxiety or loneliness
   [ ] c) The program reduced symptoms of anxiety and loneliness in the students by 60%
   [ ] d) Visits to the college counseling center increased following the intervention

7. A Danish study attributed rising autism rates in that country to which of the following factors (LO #4)?

   [ ] a) Environmental factors
   [ ] b) Greater awareness of ADHD among teachers
   [ ] c) A link to childhood vaccinations
   [ ] d) Changes in how autism is reported

8. A study of high school students in California found which of the following interventions helped prevent the development of depressive symptoms in the teens (LO #4)?

   [ ] a) Teaching students that people have the ability to change
   [ ] b) Involving students in sports activities
   [ ] c) Offering weekly group counseling sessions
   [ ] d) Scheduling monthly sessions with guidance counselors

PLEASE NOTE: WE CAN AWARD CME CREDIT ONLY TO PAID SUBSCRIBERS

THE CARLAT REPORT: CHILD PSYCHIATRY

P.O. Box 626
Newburyport, MA 01950

PRSRT STD
US Postage
PAID
Nashville, TN
Permit 989

This Issue's Focus:
ADHD

Next Time in *The Carlat Child Psychiatry Report:* Antipsychotics in Children

News of Note

Continued from page 10

All antidepressants carry a warning label cautioning users that the medications may increase the risk of suicidal thoughts and behaviors in children and young adults. The FDA required the black box warnings in 2004 after data emerged linking the drug paroxetine (Paxil) to suicidal thoughts. Opponents argue the warnings overstate the real risk and discourage physicians from prescribing them to patients who could really benefit from antidepressants.

A recent report in *Time* magazine (http://ti.me/1oHlaCw) interviewed 17 leaders in the psychiatry field and asked their opinions: 11 said the FDA should remove the warnings; two said the media has overblown the risk, resulting in more panic than is necessary; and four support the warning labels. Among those four, three were involved in the FDA's original decision to issue the black box warnings.

Despite the controversy, the FDA has no plans to reconsider the warnings, according to the *Time* article.

❖ ❖ ❖