

# FDA Panel: ADHD Patch Backed With Caution

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GAITHERSBURG, MD. — A federal advisory panel has supported approval of a transdermal methylphenidate patch for treating attention-deficit hyperactivity disorder in children—with a caveat.

Because of the patch's potential to cause sensitization to methylphenidate, the Food and Drug Administration's Psychopharmacologic Drugs Advisory Committee agreed that an approval should include a warning about this link.

The possibility of sensitization elicited concern among panel members, because a patient who becomes sensitized can never take methylphenidate in any form again.

At a meeting last month, the committee unanimously agreed that the patch was effective for treating ADHD in children aged 6-11 years. That is the indication proposed by Shire Pharmaceuticals Inc. and Noven Pharmaceuticals Inc., the companies that codeveloped it.

In addition, the panel voted 11-1 against an overt restriction that would limit the use of the patch to children who are unable to take oral formulations. Instead, it supported the idea of including language in the label advising prescribers to consider other treatment options that do not pose the same risk of sensitization before considering the transdermal formulation.

Dr. Thomas Laughren, director of the FDA's division of psychiatry products in Rockville, Md., said such wording could take the same approach as language in a section of the label for the atypical antipsychotic ziprasidone (Geodon). Unlike other atypicals on the market, the in-

dications and usage section in ziprasidone's label (or package insert) includes the statement: "When deciding among the alternative treatments available for this condition, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs."

The frequency of sensitization in people treated with the patch is uncertain, based on the data available. In trials, there was one report of an allergic reaction in a patient who stopped using the patch because of irritation at the site of the patch that reappeared at the same site after starting on oral methylphenidate, a sign of contact sensitization, said Dr. Raymond Pratt, vice president of clinical development at Shire. The oral medication was then discontinued. The frequency of this kind of reaction is difficult to quantify, he told the panel.

Another concern was how a physician could distinguish between local skin irritation and signs of sensitization, which FDA officials said would be explained in the label.

The panel chair, Dr. Wayne Goodman, said he would vote in favor of safety but recommended that a warning be included in the label until more data are available on this issue. The difficulty in predicting prevalence was troubling, and he and other panel members supported postmarketing surveillance of children treated with the patch to resolve this issue, said Dr. Goodman, chair of the department of psychiatry at the University of Florida, Gainesville.

Dr. Daniel Pine, the panelist who voted in favor of restricting the indication to children for whom oral methylphenidate is not an option, said he was satisfied with the efficacy data.

However, language similar to that in the ziprasidone label would be too weak, and it would be better to err on the side of caution. It would be a "potential disaster" if a proportion of patients with ADHD could not take methylphenidate, remarked Dr. Pine, chief of child and adolescent research in the mood and anxiety disorders program at the National Institute of Mental Health, Bethesda, Md.

If approved, the thin, transparent patch will be available in 10-mg, 16-mg, 20-mg, and 27-mg strengths, providing dose ranges over 9 hours that are similar to the oral sustained formulation of methylphenidate, according to Shire.

The manufacturers submitted an application for approval in 2002, but in 2003 the FDA decided not to approve the patch because of concerns over excessive methylphenidate exposure at inappropriate times and an unacceptable safety profile, which included a high rate of insomnia, anorexia, and weight loss associated with the patch, based on studies in which it was worn for 12 hours. The company then conducted studies of the patch with a 9-hour wear time and resubmitted the application for approval in June.

In the two studies of children aged 6-12 years with ADHD—a 2-day laboratory classroom study of 93 children and a pivotal multicenter outpatient study of 274 children that compared the patch with Concerta and placebo over 7 weeks—significant improvements in behavior were seen within 2 hours of application of the patch (left on for 9 hours) and persisted for 3 hours after removal, according to Shire. About 55% of patients developed some skin irritation at the patch site, but there were few discontinuations because of application site reactions, Dr. Pratt said. ■

## Asperger's Disorder, High-Functioning Autism Often Overlap

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WASHINGTON — Officially, the lack of delayed language skills is what separates a child with Asperger's disorder from one with high-functioning autism. But the reality is far more complex, Dr. Chris Plauche Johnson said at the annual meeting of the American Academy of Pediatrics.

Both Asperger's disorder and autism are included in the Diagnostic and Statistical Manual-IV, Text Revision (DSM-IV-TR) under "Pervasive Developmental Disorders," a term which itself is now falling out of use in favor of "autism spectrum disorders." Asperger's disorder is a unique diagnostic category in DSM-IV-TR, while children who meet the criteria for autism except for having normal intelligence are often classified under "atypical autism."

Both Asperger's and high-functioning autism share criteria regarding social skills and restricted interests, but they differ in language ability and age of onset. However, not everyone agrees that the two are actually separate entities, and some experts feel the DSM-IV-TR criteria for Asperger's disorder are too restrictive, said Dr. Johnson, a developmental pediatrician and clinical professor of pediatrics at the University of Texas Health Science Center, San Antonio.

The American Academy of Pediatrics plans to issue a revised clinical report on autism spectrum disorders sometime in 2006-2007, she said.

Unlike autism, for which the parents' first concern is about language development and which arises when the child is 18-24 months old, parents of children with Asperger's disorder often don't become

concerned until the child is in preschool and has difficulties with peer social interactions or in general behavior.

But the syndromes are beginning to blend now that comorbid mental retardation is being diagnosed less and less often among children with autism. Before 1990, about 90% of autistic children also had mental retardation. Now the rate has dropped to 50% or even lower in some studies. A major reason for this is that better diagnostic tools and improved clinician training have reduced the number of children whose intelligence was considered "untestable" and who therefore were listed as mentally retarded.

These days, it's highly unusual for a child to be considered untestable, which calls into question the whole phenomenon of atypical autism. "High-functioning autism may not be atypical in the new millennium," Dr. Johnson said.

But even children with high-functioning autism have delayed speech, with few words or with inconsistent, "pop-up" use of words. They may be able to label things or repeat song lyrics or phrases, but have difficulty constructing meaningful sentences on their own. They often don't respond to verbal or body language cues from others, and may interrupt others. In contrast, children with Asperger's disorder have no significant delay in language.

Any child suspected of having either disorder should be referred for comprehensive testing so that interventions such as speech and social skills training can begin early. In the end, the diagnosis may hinge on practical issues: Insurance companies, for example, will usually pay for therapy for autism but not always for Asperger's. ■

### How the Criteria Delineate the Two

According to the DSM-IV-TR, criteria for autism and Asperger's disorder include:

In both autistic disorder and Asperger's disorder, there is qualitative impairment in social interaction, as manifested by at least two of the following:

- Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction.
- Failure to develop peer relationships appropriate to developmental level.
- A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people.
- Lack of social or emotional reciprocity.

In both autistic disorder and Asperger's disorder, there are restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

- Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus.
- Apparently inflexible adherence to specific, nonfunctional routines or rituals.
- Stereotyped and repetitive motor mannerisms (hand or finger flapping or twisting, or complex whole-body movements).

d) Persistent preoccupation with parts of objects.

In autistic disorder, there are qualitative impairments in communication as manifested by at least one of the following:

- Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime).
- In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others.
- Stereotyped and repetitive use of language or use of idiosyncratic language.
- Lack of varied, spontaneous, make-believe play or social imitative play appropriate to developmental level.

Conversely, in Asperger's disorder, there is no clinically significant general delay in language (single words used by age 2 years, communicative phrases by age 3 years).

Although not specified in the DSM-IV, children with autistic disorder who have IQs higher than 70 are often classified as having "high-functioning autism."

The criterion for high-functioning autism is sometimes considered to be an IQ greater than 85 or even greater than 100.