Prodromes—premonitory symptoms or clinical signs prior to the actual onset of disease—may be a useful target for early intervention. Research has begun to identify prodromal states as well as endophenotypic markers (i.e., heritable biological traits that are present regardless of whether an individual is symptomatic) that may help to identify children in whom a disorder is likely to develop. A literature review was undertaken to characterize specific markers for bipolar disorder and to provide an update.

Early temperamental markers may signal that an individual could be at risk if exposed to certain stressors. Among these temperamental markers are behavioral disinhibition, certain sleep abnormalities, depression, and poor emotion regulation.

Identified endophenotypic markers include: difficulty in labeling emotions from facial expressions; verbal memory and executive function deficits; and the combination of deficits in visual-spatial abilities with high arithmetic abilities. HPA axis activity dysregulation indicated by elevated afternoon cortisol levels has also been reported, as have differences in brain morphology compared with healthy children.

A retrospective study of children with bipolar disorder found more than half experienced a lengthy mania prodrome (>1 year) that had a slow onset and was characterized by sub-threshold depressive and manic symptoms as well as general psychopathology. A shorter-lasting, subacute prodrome was found in another 44%. A range of clinical features were found that characterized the bipolar prodromal state (see box) in high-risk
children. Studies have found that many children and adolescents (20–49%) with diagnosed major depressive disorder later convert to bipolar disorder.

Potential treatments during prodromal periods have received little investigation. A few uncontrolled studies of drug therapies have been conducted in children with milder variants and/or other Axis I disorders thought to be at high risk for bipolar disorder. Results have been promising, but the adverse effects of mood stabilizers in children are problematic. Early research suggests psychotherapies may be helpful, particularly Family Focused Therapy.

Luby J, Navsaria N: Pediatric bipolar disorder: evidence for prodromal states and early markers. Journal of Child Psychology and Psychiatry. Published online January 18, 2010 at www.interscience.wiley.com; doi 10.1111/j.1469-7610.2010.02210.x. From Washington University School of Medicine; St. Louis, Mo. Funded by the NIMH. The authors declare they have no conflicts of interest.

Diagnosing Bipolar Disorder

A survey of child and adolescent psychiatrists found most relied on symptoms other than those in the DSM to lead them to consider a diagnosis of bipolar disorder. Nearly half felt the DSM episode requirement was inappropriate.

Methods: A random sample of 100 members of the American Academy of Child and Adolescent Psychiatry were selected in 5 geographic areas chosen because they included major research groups with expertise in bipolar disorder. The 53 physicians who agreed to participate underwent a 30-minute phone interview during which they provided demographic and practice-specific information as well as a list of 10 symptoms that would lead them to consider a bipolar disorder diagnosis. They were also asked to rank the importance of those symptoms. Reported symptoms were then categorized into 21 clusters (see box); 8 of which reflected DSM-IV-TR criteria.

Results: Doctors named a total of 193 symptoms. The most frequently cited were: lability (62%); irritability (62%); grandiosity (60%); aggression (59%); racing thoughts (57%); and pressured speech (57%). They rated lability, grandiosity, family history, aggression, and expansive or euphoric mood as the most important factors in making the diagnosis. Physicians with less expertise and lower confidence levels tended to endorse more DSM criteria.

Discussion: Most survey respondents had an academic affiliation, and private practitioners may have been underrepresented. The results thus can not be generalized to all child and adolescent psychiatrists. In addition, the study was not adequately powered to detect influences of physician characteristics on diagnostic practices.

Cognitive Precursors to Schizophrenia

A longitudinal study found specific cognitive deficits are identifiable before puberty in children in whom schizophrenia develops, and that their cognitive development lags behind healthy peers and children eventually diagnosed with major depression.¹

Background: Cognitive deficits are well established in schizophrenia but the developmental trajectory of premorbid deficits is unclear. Adult schizophrenia may be preceded by a decline in cognitive function (developmental deterioration), cognitive deficits may appear early and remain static in the premorbid period (developmental deficit), or children may experience gains in cognitive function that lag behind those of their peers (developmental lag).

Methods: A regional birth cohort of >1000 children born in New Zealand in 1972 and 1973 has been followed to age 32 years (n=972). IQ tests were administered to all participants at ages 7, 9, 11, and 13 years. Trajectories of verbal reasoning, visuospatial problem solving, working memory, attention, and processing speed between 7 and 13 years were retrospectively compared among 35 children later diagnosed with schizophrenia; 145 children later diagnosed with depression; and 556 children in whom no psychiatric disorder developed.

Results: Early IQ deficits were evident in children who went on to develop schizophrenia or depression, compared with mentally healthy children. Deficits were greater in the preschizophrenic patients. Specifically, preschizophrenic children showed early impairment in verbal reasoning, knowledge acquisition, and concept formulation that persisted into adolescence. In addition, these children showed a developmental lag (behind healthy peers and those later developing depression) in working memory, visuospatial problem solving skills, processing speed, and attention. Children later diagnosed with depression also showed developmental deficits, but their pattern of cognitive lags differed.

Discussion: Children in whom schizophrenia eventually developed showed early struggles with verbal reasoning and lagged behind their peers in attention and working memory as they aged. These findings support early and enduring genetic or acquired vulnerabilities to the disease. However, the clinical implications in terms of early identification and treatment are unclear, and it should be noted that the children began to deteriorate as they entered adolescence and likely began experiencing prodromal symptoms.²

¹Reichenberg A, Caspi A, Harrington H, Houts R, et al: Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. American Journal of Psychiatry 2010;167 (February):160–169. From Duke University, Durham, N.C.; and other institutions. Funded by the U.K. Medical Research Council; the NIMH; and other not for profit sources. Three study authors disclosed commercial relationships with industry sources; all others reported no commercial relationships.

²Kates W: Investigating the cognitive antecedents of schizophrenia [editorial]. American Journal of Psychiatry 2010;167 (February):122–124. From the State University of New York, Syracuse. Dr. Kates has no commercial relationships that might pose a conflict of interest.

OROS Methylphenidate Does Not Impair Sleep

Insomnia affects about 3–5% of methylphenidate-treated patients depending on the formulation.¹ In a small manufacturer-sponsored study OROS methylphenidate (Concerta) did not negatively affect sleep parameters.²

Methods: Stimulant-naïve children aged 6–12 years with at least moderately severe ADHD (n=24) received 6 weeks of open-label flexibly dosed OROS methylphenidate. Starting dosages were 18 mg/day for patients weighing <55 lbs and 27 mg/day for those weighing ≥55 lbs. Final dosages ranged from 18 to 45 mg/day. Concomitant medications that could affect sleep were prohibited. ADHD symptoms were evaluated using standardized
measures and sleep architecture was measured by polysomnography and parental sleep questionnaires at baseline and study end.

**Results:** The mean patient age was 8 years and 22 of the 24 patients were male. None of the children met polysomnographic criteria for obstructive sleep apnea or periodic limb movement disorder at baseline. ADHD symptoms improved and 71% of participants responded to treatment.

Repeat polysomnography after 6 weeks of OROS methylphenidate treatment showed the number of awakenings per night significantly decreased from 15 to 12 (p=0.047) and the percentage of stage II sleep increased from 40 to 43% (p=0.02). Mean sleep onset latency increased from 18 to 29 minutes (p=ns); this change was likely due to 3 children with significant increases of >1 hour. Other polysomnographic measures showed no significant change. Subjective sleep measures including total sleep time, sleep onset delay, nighttime awakenings, and others did not change significantly with OROS methylphenidate treatment.

Six children reported sleep problems while taking OROS methylphenidate. They were significantly younger than those without sleep complaints (7 vs 9 years) and had higher baseline ADHD-related symptom scores, but medication dose did not differ significantly. Bedtime resistance and sleep onset delay increased in these 6 patients.

**Discussion:** These results suggest OROS methylphenidate does not have negative effects on sleep in children with ADHD. However, because the study sample was small and there was no placebo control, the results need to be replicated in larger, more rigorous studies.

1 Facts & Comparisons eAnswers.

### Olanzapine Concerns in Adolescents

Eli Lilly and the FDA have updated safety information on olanzapine (Zyprexa) use in adolescents. Compared with adult patients, metabolic effects including weight gain and increases in cholesterol and triglycerides are generally greater in adolescents treated with olanzapine. The incidence of hyperprolactinemia, galactorrhea, and gynecomastia are also higher in adolescents than adults, and liver enzyme elevations may be greater. Rates of treatment-associated sedation are also higher in adolescents. Physicians are urged to consider the long-term effects, particularly of weight gain and hyperlipidemia, when choosing antipsychotic treatment for young patients. According to the updated label, “in many cases this may lead them to consider prescribing other drugs first in adolescents.”


### Prevalence of Mental Health Disorders

Data from 3042 children aged 8–15 years who participated in the National Health and Nutrition Examination Survey (NHANES) in 2001–2004 was used to estimate the prevalence and clinical correlates of mental health disorders in young people as well as rates of service use. NHANES surveyed a nationally representative sample of children and adolescents in person and follow-up surveys were administered to their parents by phone.

Overall, 1 in 8 children had at least 1 mental health disorder, but only half were treated (see table, next page). Rates were higher in boys than in girls, primarily because of a high rate of ADHD in boys. Girls had a 2-fold higher rate of mood disorders. Conduct disorder and
mood disorders were common in older youths (aged 12–15 years), while ADHD was more prevalent in the younger group (aged 8–11 years). Lower income was associated with a greater prevalence of any mental health disorder. About 14% of children had comorbid mental health disorders. Significant associations were found between ADHD and conduct disorder (odds ratio* [OR], 7.6), ADHD and mood disorders (OR, 3.4), and generalized anxiety and panic disorders (OR, 29.5). These appear to be the first published prevalence estimates of mental health disorders in the general U.S. population of children and adolescents. Additional NHANES surveys covering a wide variety of conditions were conducted between 2004 and 2009.

**Extended Treatment With Atomoxetine**

Adolescents treated with atomoxetine (Strattera) for ADHD experienced continued benefit during 40 weeks of maintenance therapy.

**Methods:** Two atomoxetine titration schedules and 2 maintenance doses were compared in adolescents aged 13–15 years. Following a washout of previous stimulants (>50% of patients), patients were randomly assigned to 8 weeks of atomoxetine with fast titration (0.5 mg/kg/day for a minimum of 3 days, followed by 1.2 mg/kg/day) or slow titration (0.5 mg/kg/day for 7–9 days, 1.0 mg/kg/day for 7–9 days, and then 1.2 mg/kg/day). Tolerability was assessed at 4 weeks when all patients were receiving 1.2 mg/kg/day. Those who responded to acute treatment were then randomized to a maintenance dose of 0.8 mg/kg/day (low dose) or 1.4 mg/kg/day (the labeled maximum). Efficacy was measured using the ADHD Rating Scale (ADHD-RS).

**Results:** A total of 267 adolescents completed the titration phase and 178 were re-randomized to maintenance treatment. Of the patients who did not continue, 28% did not meet response criteria and the remainder dropped out because of side effects or for other reasons.

During acute treatment ADHD-RS total scores decreased from 35 to 18 in the fast titration group and from 33 to 16 in the slow titration group (p<0.001 compared with baseline). The titration schedules were equally well tolerated. During the 40 weeks of ongoing therapy there was a small but significant increase in ADHD-RS inattention scores indicating a loss of benefit during the maintenance phase. The change was more pronounced with the lower atomoxetine dose on hyperactive/impulsive scores. Final ADHD-RS total scores were 17 with the 0.8 mg/kg/day maintenance dose and 15 with the 1.2 mg/kg/day dose. Side effects during maintenance therapy were similar in the 2 dosage groups and included nausea, dizziness, and arthralgia. Dizziness affected only patients treated with the lower dose.

Social, family, and academic outcomes were also measured during atomoxetine treatment. Family strengths and weaknesses, adaptive functioning related to ADHD treatment, and

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Population Prevalence</th>
<th>Mental Health Service Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>11.3%</td>
<td>50%</td>
</tr>
<tr>
<td>ADHD</td>
<td>7.8%</td>
<td>48%</td>
</tr>
<tr>
<td>Mood Disorders</td>
<td>2.9%</td>
<td>44%</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>1.7%</td>
<td>46%</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>0.4%</td>
<td>32%</td>
</tr>
</tbody>
</table>

*Reference Guide Item.

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Merikangas K, He J-P, Brody D, Fisher P, et al: Prevalence and treatment of mental disorders among US children in the 2001–2004 NHANES. *Pediatrics* 2010;125 (January):75–81. From the NIMH; and other institutions. **NHANES was Funded by the NIH. The authors report they have no commercial relationships relevant to this article.**
some academic achievements improved significantly. Grade point averages improved, though not significantly. Patients showed little change on a scale measuring behavioral risks, except for a decline in unintentional injuries.

**Discussion:** These observations suggest that ADHD symptom reduction occurs during acute treatment with atomoxetine, and there is no advantage of using a slower titration schedule. Benefits are better maintained during ongoing therapy with a 1.4 mg/kg/day dose, and long-term treatment continues to influence social and academic development.

**Study Rating*—17 (100%):** This study met all criteria for a randomized clinical trial. However, an important limitation acknowledged by the authors is the lack of a placebo control. In their view, ethical concerns prevented administering a placebo during the extended period of maintenance treatment.

Wietecha L, Williams D, Herbert M, Melmed R, et al: Atomoxetine treatment in adolescents with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2009;19 (December):719–730. From Lilly USA, LLC, Indianapolis, Ind.; and other institutions. **Funded by Eli Lilly. All of the study authors disclosed commercial relationships with Eli Lilly, including 3 who are employed by Lilly USA.**

*Reference Guide Item.

### Reference Guide

**Odds Ratio:** A comparison of the probability of an event in two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.