Disturbed sleep in infants and toddlers is associated with symptoms of anxiety and depression at age 3 years, according to a longitudinal study.

**Background:** Previous studies have established an association of childhood sleep problems with anxiety and depression but were mainly conducted in school-aged children and did not account for earlier emotional symptoms that could affect sleep.

**Methods:** The analysis was conducted in the Generation R Study cohort of children born in Rotterdam, the Netherlands, in 2002–2006. Parents were asked about the presence of 4 specific sleep problems and 3 sleep-related parent behaviors when the children were 2 months old and again at 24 months. Anxiety and depressive symptoms were assessed at ages 1.5 and 3 years using the Child Behavior Checklist for toddlers. Children scoring in the upper 20th percentile of the 8-item Anxious/Depressed syndrome scale at age 3 years were identified as having these emotional problems. Data were analyzed for 4782 children.

**Results:** Anxiety and depression at age 3 years were associated with dyssomnia (greater number of nighttime awakenings) at both 2 and 24 months. Emotional symptoms were associated with shorter total sleep duration at 24 months but not 2 months. Parasomnia (nightmares) was not assessed at 2 months but, in the toddlers, was predictive of anxiety and depression. These associations remained significant after statistical adjustment for various family covariates, and they were independent of the level of anxious/depressed symptoms already present at age 2 years. The fourth sleep symptom, lack of rhythmicity (that is, lack of a stable sleep pattern) was not associated with later anxiety or depression.

Of the sleep-related parental behaviors assessed, lack of a set bedtime in 2-year-olds was a risk factor for anxiety and depression at age 3 years, regardless of whether these symptoms were present at age 2 years. Infants and toddlers who usually fell asleep with their parents in the room also had increased risk for later anxiety or depression.

**Discussion:** Short sleep duration and frequent awakenings may disturb the function of the hypothalamic-pituitary-adrenal axis or interfere with the development of neurons that control...
daytime vigilance. The present findings suggest that clinicians should be alert for sleep problems in young children and for parenting behaviors suggesting poor sleep hygiene, although possible effects of intervention are untested.

Jansen P, Sardijan N, Hofman A, Jaddoe V, et al: Does disturbed sleeping precede symptoms of anxiety or depression in toddlers? The Generation R Study. Psychosomatic Medicine 2011; doi 10.1097/PSY.0b013e31820a4abb. From Erasmus Medical Center-University Medical Center Rotterdam, the Netherlands. Funded by Erasmus Medical Center-University Medical Center Rotterdam; and other sources. The authors disclosed no competing interests.

Early Menarche Linked to Depressive Symptoms

Girls who experienced early menarche were more likely than their peers to have depressive symptoms in mid-adolescence, according to a longitudinal study.

Methods: Study participants were members of a southwestern British birth cohort, born in 1991 and 1992 and enrolled in an ongoing child health and development study. Complete data were available for about 2000 girls. To measure depressive symptoms, girls were administered the Short Mood and Feelings Questionnaire (SMFQ) during visits to the study clinic at average ages of 10.5, 13, and 14 years. Age at menarche was determined via annual questionnaires completed by mothers. The mean age at menarche in this sample was 12.5 years. Early and late menarche were defined as 1 standard deviation above or below the average—11.5 and 13.5 years, respectively.

Results: At age 10.5 years, girls in all 3 groups had a similar level of depressive symptoms, with mean SMFQ scores near 3.5 in each group. By age 13 years, those with early menarche had a higher level of depressive symptoms than the other groups. The between-group difference was moderate but statistically significant (p=0.007). By age 14 years, the 3 groups had clearly separated with SMFQ scores of 6.1, 5.1, and 4.4 in the early, normative, and late menarche groups, respectively (p<0.001). The differences between groups remained consistent after adjustment for potential confounding factors (e.g., socioeconomic status, body mass index, family breakdown).

Discussion: These observations support an early timing hypothesis that suggests girls who mature early are more vulnerable to psychological distress. Girls with early menarche may feel deviant, isolated, and faced with demands with which they are not developmentally ready to cope.


Trauma and Early Psychotic Symptoms

Maltreatment by an adult and bullying by peers during childhood were associated with the development of delusions or hallucinations, according to a longitudinal study.

Methods: Study participants (n=2127) were a nationally representative British birth cohort of twins born in 1994 or 1995. Mothers were interviewed about trauma during home visits when the children were aged 5, 7, 10, and 12 years. Specifically, mothers were questioned about whether the children had experienced punishment severe enough to induce harm, maltreatment by a non-parental adult, bullying, and accidental injury. Children were also interviewed privately at age 12 years and were asked whether they had been bullied and questioned about possible delusions and hallucinations. Children were classified as symptomatic only after additional probing to determine whether or not the experiences were plausibly real.

Results: At age 12 years, 6% of children had at least 1 definite psychotic symptom. All types of trauma were associated with the symptoms, but the association was particularly strong for trauma associated with intention to harm (i.e., mistreatment by an adult and bullying). Psychotic
symptoms were also linked with other factors, such as socioeconomic deprivation, low IQ, and genetic risk, but the association with trauma was not accounted for by these other factors.

A total of 28% of children were maltreated or bullied before age 12 years, and 3% experienced both types of trauma. Those who had either type of trauma with intent to harm were more than 3 times as likely as others to have psychotic symptoms, and those with both types of trauma were nearly 6 times as likely. The effect of trauma was similar whether it occurred before age 7 years or was limited to later childhood. Accidental injury was also associated with psychotic symptoms, but the effect was relatively weak.

**Discussion:** Adolescents who report psychotic symptoms are at increased risk for psychotic illness later in life. Results of this study suggest that childhood maltreatment and bullying may contribute to the development of symptoms, independently of genetic risk and other predisposing factors. Assessment of trauma should be part of clinical interviews of children with early symptoms of psychosis.


### PDD Improvement with Progesterone

Progesterone, given to regulate the menstrual cycle, resulted in striking improvement of behavior in a girl with pervasive developmental disorder not otherwise specified (PDD-NOS).

The patient had a history of extreme and worsening impulsivity, hyperactivity, inattention, and restlessness since age 4 years. At age 6 years, she exhibited low IQ and poor language skills and she received diagnoses of PDD-NOS, ADHD-like symptoms, expressive/receptive language disorder, and mild mental retardation. Several medication trials failed to regulate her mood and attention, and she was hospitalized with severe anxiety, disjointed thinking, temper tantrums, insomnia, and self-injurious behavior. She was discharged after showing some improvement on clonidine, dexmethylphenidate, and aripiprazole.

At age 11 years, the patient experienced menarche. Because menstruation was prolonged and heavy, she was prescribed medroxyprogesterone injections. Within 4 weeks of her first injection, she showed significant improvement in mood, behavior, and cognition. She stopped cutting herself and was able to participate in group activities and maintain friendships. Now 12 years old, she continues to benefit from the injections every 10 weeks along with her other medications.

This appears to be the first report of response to progesterone in a child with PDD. Although there are several possible explanations, including a potential effect of changes in medication administration timing, it seems likely that her improvement was a neurochemical effect of progesterone. Progesterone and other neuroactive steroids affect pre- and postsynaptic receptors and induce release of glutamate and GABA. These effects occur in brain regions involved in learning, memory, emotion, motor skills, and cognition. Studies of GABA receptor modulators like progesterone have shown opposing effects: low concentrations produce anxiety, irritability, and mood swings, while higher concentrations have positive effects on mood and anxiety. Progesterone acts in a way similar to oxytocin, which has shown positive effects in autism.

Gbadebo O: Reduced maladaptive behavior and improved social and communicative function in a child with pervasive developmental disorder—not otherwise specified (PDD-NOS) treated with progesterone. *Clinical Medicine and Research* 2011; doi 10.3121/cmr.2010.942. From the Marshfield Clinic, Wis. The author did not include disclosure of potential conflicts of interest.

**Drug Trade Names:** aripiprazole—Abilify; clonidine—Catapres; dexmethylphenidate—Focalin; medroxyprogesterone injection—Depo-Provera; oxytocin—Pitocin
Sertraline Ineffective for PTSD

In a manufacturer-sponsored controlled trial, sertraline was not superior to placebo in pediatric posttraumatic stress disorder. The trial was terminated early after an interim analysis showed that further patient accrual was unlikely to produce a positive result.

**Background:** Sertraline has demonstrated efficacy in adults with noncombat-related PTSD but not in veterans with combat-related illness. The efficacy of SSRIs in pediatric PTSD has not received much study. Two small, uncontrolled trials suggested citalopram may be effective.

**Methods:** This 21-center study enrolled patients, aged 6–17 years, who met DSM-IV criteria for PTSD. During a 2-week screening period, all patients underwent 3 sessions of psychoeducation and cognitive-behavioral therapy. Those who did not improve sufficiently were randomly assigned to 10 weeks of double-blind treatment with flexibly-dosed sertraline (50–200 mg/day) or placebo. No further psychotherapy was provided. Patients had been ill for an average of more than 2 years before enrollment; yet fewer than 10% had received previous drug therapy, and 25% had received psychotherapy. The primary efficacy outcome was the UCLA Post-Traumatic Stress Disorder Index (UCLA PTSD-I), a semi-structured interview that rates the severity of 22 symptoms; scores can range from 0 to 68.

**Results:** Change in UCLA PTSD-I score did not differ between the sertraline (n=67) and placebo (n=62) groups. Mean baseline scores were 44 and 42, respectively. In the endpoint last observation carried forward analysis, final scores were 26 with sertraline and 22 with placebo. Improvements on most secondary outcome measurements including the Clinical Global Impressions Severity and Improvement scales and rating scales for stress symptoms, depressive symptoms, and quality of life also did not differ between the groups. For several secondary endpoints, patients showed greater improvement with placebo than with sertraline. Response rates were 51% for sertraline and 57% for placebo. Sertraline was generally safe and well tolerated. However, 7 patients who took sertraline and 4 who took placebo reported new or worsening suicidal thoughts.

**Discussion:** Placebo response is common in studies of pediatric drug treatment. The authors suggest this may partially explain the negative findings of the present study.

**Study Rating**—17 (100%): This study met all criteria for a controlled trial.


From Children’s National Medical Center, Washington, D.C.; Columbia University College of Physicians and Surgeons, New York, N.Y.; and Pfizer, Inc. **Funded by Pfizer. Several study authors disclosed financial relationships with commercial interests.**

**Drug Trade Names:** citalopram—Celexa; sertraline—Zoloft

Drug-Related Suicide Attempts in Adolescents

The Drug Abuse Warning Network (DAWN) project monitors drug-related emergency department (ED) visits in the U.S. Using data from this project, the Substance Abuse and Mental Health Services Administration examined drug-related adolescent suicide attempts between 2004 and 2008.

On average, more than 178,000 annual ED visits were associated with a drug-related suicide attempt in a patient aged ≥12 years. Attempts were substantially more common among females than males (15,552/year vs 5283/year). Nearly all attempts (95%) included a pharmaceutical...
agent, most often anxiolytics (26%), acetaminophen products (24%), and antidepressants (23%). Alcohol, sometimes in combination with other drugs, was involved in 11% of suicide attempts, and illicit substances were involved in 9%. There was no evidence of follow-up care after ED discharge for about 23% of all patients who attempted suicide.2

Because depression, which may be a risk factor for suicide, can worsen in the fall or around major holidays, seasonal variations in suicide attempts were also tracked. In the population as a whole, there was little seasonal variation in suicide attempts. However, male adolescents were more likely to attempt drug-related suicide in December. Nearly 19% of all drug-related suicide attempts by males occurred in December. The rate for females was relatively steady throughout the year.

The study did not address reasons behind the adolescents’ suicide attempts. However, a previous suicide attempt is a significant predictor of future attempts. Knowledge of the patterns found in the study could be useful for suicide prevention programs.


Nicotinic Modulator Ineffective in Pediatric ADHD

An investigational partial nicotinic receptor agonist, ABT-089, had no effect on ADHD symptoms in 2 randomized trials in children. These results contrast with the previously demonstrated efficacy of the agent in adult ADHD.

Background: Several types of evidence suggest the involvement of nicotinic cholinergic signaling in ADHD. In-utero nicotine exposure is a risk factor for ADHD, the disorder increases risk of cigarette smoking, and self-administered nicotine ameliorates the symptoms of ADHD. A new class of agents has been developed that selectively modulate nicotinic cholinergic signaling.

Methods: The 2 trials enrolled children, aged 6–12 years, with ADHD of at least moderate severity. Participants were randomly assigned to 6–8 weeks of treatment with ABT-089, placebo, or atomoxetine (Strattera) used as a positive control. ABT-089 dosing was based on tolerability data extracted from the adult studies and ranged from <0.1 mg/kg/day to 1.4 mg/kg/day. Response was evaluated by clinicians using the ADHD Rating Scale-IV, Home Version, and the Clinical Global Impressions-ADHD Severity scale.

Results: A total of 387 children received at least 1 dose of study medication and were included in the analysis. There were no significant differences in ADHD Rating Scale score changes between the ABT-089 and placebo groups. ABT-089 also did not differ from placebo with regard to the secondary study outcomes, nor did it differ in separately analyzed subgroups of treatment-naïve or previously treated patients. Atomoxetine demonstrated the expected efficacy and adverse effects, suggesting that the lack of response to ABT-089 was not due to faulty study design or execution. ABT-089 did not differ from placebo in safety or tolerability.

Discussion: Because children had plasma levels of ABT-089 similar to those seen in adults, it is unlikely that the lack of effect in children was the result of inadequate dosing. It is possible that the pharmacokinetics or dynamics of this agent differ between children and adults or that the basic characteristics of ADHD may change with age. Given the likelihood
that other new agents in this class will be investigated in children, the tolerability of ABT-089 may be encouraging.

**Study Rating**—17 (100%): These studies met all criteria for randomized controlled trials.


*See Reference Guide.

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**Reference Guide**

**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.

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**Course Schedule for Activity Code 10MP02C / Exam #17**

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**Target Audience**

This activity is intended for physicians and other healthcare providers who are involved with or have an interest in the diagnosis and management of child and adolescent psychiatric disorders.

**Learning Objectives**

- Integrate into clinical practice findings from new diagnostic and therapeutic studies.
- Determine appropriate patient evaluation and treatment selection for child and adolescent psychiatric and behavioral disorders.
- Discuss developmental risk factors and comorbid disorders and how they affect outcomes.
- Plan strategies for early intervention to improve outcomes.
- Appropriately prescribe medications or other therapeutic interventions.
- Recognize and implement new approaches to the treatment of child and adolescent psychiatric and behavioral disorders.

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