

# CHILD & ADOLESCENT PSYCHIATRY ALERTS

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## Sleep Variables and Suicidal Behavior

In a longitudinal study of adolescents, frequent nightmares were associated with a nearly 2-fold increase in suicide attempts and a 50% increase in nonsuicidal self-injury (NSSI). Other sleep disturbances were not associated with these outcomes.

**Background:** Evidence has suggested that sleep problems are associated with suicidal behavior in clinical and general population samples, but results for specific variables have been inconsistent. In adolescents, nightmares appear to be a common but underreported problem that could potentially be preventable with treatment.

**Methods:** Participants were adolescents from junior high and high schools in a single Chinese province who were enrolled in a longitudinal study of health and behavior. Baseline questionnaires, completed by subjects in grades 7, 9, and 11, included questions about lifetime and recent suicidal thoughts, plans, and attempts; NSSI; sleep duration; and sleep problems. The questionnaire identified nightmares as emotionally intense, frightening, and vivid dreams that woke the subject. A few nightmares per month was considered frequent. Participants were also assessed for anxiety and depressive symptoms, impulsiveness, and individual and family demographic factors. Follow-up questionnaires were administered after 1 year.

**Results:** More than 7,000 adolescents completed the baseline and follow-up questionnaires. At baseline, 14% reported insomnia symptoms and 25% rated their sleep quality as poor or very poor. Nearly 42% reported having nightmares several times in the past year, and 9% had nightmares several times a month.

At the follow-up assessment, 10% of patients reported having suicidal thoughts in the previous year, 4% reported suicidal plans, 3% reported suicide attempts, and 9% reported NSSI. After adjusting for multiple covariates, only the association between nightmares in the past year and suicide attempts was significant (adjusted odds ratios,\* 1.66 for nightmares several times per year and 1.96 for frequent nightmares). Additional adjustment for other sleep variables did not influence this association. Nightmares were also associated with higher rates of NSSI (adjusted odds ratios, 1.31 for nightmares several times a year and 2.52 for frequent nightmares).

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Multiple other sleep variables had univariate associations with suicidal behavior or NSSI, but these associations did not survive statistical adjustment. Girls had more frequent nightmares than boys, as well as higher rates of suicidality and NSSI, and a stronger association of these outcomes with nightmares.

**Discussion:** The mechanisms associating nightmares with suicidal behavior are unclear and probably multifaceted. Suicide attempts and self-harm may be a coping behavior to reduce nightmare distress, or both phenomena may reflect stressful life events, chronic stress, or an underlying problem such as depression, PTSD, or substance dependence. Regardless of the etiology, the present results suggest that assessment for nightmares as a modifiable risk factor for suicide or self-harm could aid in the early identification of adolescents at risk.

Liu X, Lui Z, Chen R, Cheng X, et al: Nightmares are associated with future suicide attempt and non-suicidal self-injury in adolescents. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.18m12181. From Shandong University School of Public Health, China; and other institutions. **Funded by the National Natural Science Foundation of China. The authors declared no competing interests.**

\*See Reference Guide.

## Persistent Irritability in ADHD and Later Depression

In children with ADHD, chronic irritability that persists into adolescence is associated with development of depression, according to the results of a longitudinal study. This finding suggests that irritability should be monitored in children with ADHD, as those who remain irritable beyond childhood may be at particular risk and could benefit from preventive interventions.

**Methods:** The study group consisted of children and adolescents who participate in the British Study of ADHD, Genes and Environment (SAGE). All had a clinical diagnosis of ADHD and also met DSM criteria for the disorder. Children aged 6–12 years at enrollment were invited to take part in a follow-up study an average of 5.4 years after initial participation. This age cutoff was chosen to limit the baseline prevalence of depression. Baseline symptoms of depression, ADHD, and irritability were measured with the parent-completed Child and Adolescent Psychiatric Assessment (CAPA). Irritability was measured with 3 CAPA items, providing a total score of 0–3. A categorical DSM-5 diagnosis of disruptive mood dysregulation disorder (DMDD) was also derived from CAPA items. In the follow-up assessment, depression symptoms were measured using the parent-completed Mood and Feelings Questionnaire (MFQ). A cutoff score on the MFQ was used to generate a binary depression rating. Irritability at follow-up was measured with the parent-completed Development and Well-Being Assessment (DAWBA), which also scores from 0 to 3. Persistent irritability was defined as a score of  $\geq 1$  on both the CAPA and the DAWBA.

**Results:** Baseline data were available for 696 children and follow-up data for 249 adolescents. At baseline the mean CAPA irritability score was 2.19, and 91% of children had  $\geq 1$  irritability symptom. Nearly one-third met diagnostic criteria for DMDD. At follow-up, the mean DAWBA score was 1.46, 64% had  $\geq 1$  irritability symptom, and 23% met diagnostic criteria for DMDD.

Depressive symptoms were above the MFQ cutoff in 54% of adolescents. Baseline irritability scores and DMDD diagnostic status were both associated with depression symptom scores, but these associations did not persist in statistical models adjusted for baseline anxiety or ADHD severity. Of children with an irritability score of  $\geq 1$  at baseline, 63% had unremitted irritability in adolescence; and the DMDD diagnosis was persistent in 37% of those affected initially. Persistent irritability, in contrast to remitted irritability, was significantly associated with depression symptom scores ( $p < 0.001$ ) and with depression scores above the cutoff (odds ratio,\* 6.35;  $p < 0.001$ ). The association of persistent irritability with depression was significant after adjustment for all available covariates.

**Discussion:** Overall, these findings suggest irritability, particularly when it persists into adolescence, may be important in the association between ADHD and depressive symptoms. It is unclear however, whether it is the persistence of childhood irritability specifically or the presence of irritability in adolescence that underlies the increased risk for depression. Regardless, children with ADHD and persistent irritability appear to be a target group for early depression prevention interventions.

Eyre O, Riglin L, Leibenluft E, Stringaris A, et al: Irritability in ADHD: association with later depression symptoms. *European Child & Adolescent Psychiatry* 2019;28:1375-1384. doi 10.1007/s00787-019-01303-x. From Cardiff University, U.K.; and the NIH. **Funded by the Wellcome Trust. The authors declare no competing interests.**

\*See Reference Guide.

## Treating Aggression in Conduct Disorder

Patients with conduct disorder (CD) who exhibit irritability and/or aggression have specific diagnostic and treatment needs. However, in spite of extensive research, evidence-based guidance is limited.

Multi-component, CBT-based, psychosocial interventions that include patient, family, and school involvement, should be used as first-line treatment. When these interventions are ineffective or the patient is noncompliant, pharmacotherapy can be considered. Although several medication classes including second generation antipsychotics, stimulants, mood stabilizers, and alpha-adrenergic agents, have been explored, the evidence is limited and generally not high quality.

A comprehensive review suggests efficacy of second generation antipsychotics in the treatment of aggression in CD is limited. Additionally, adverse effects hinder their use, and short-term treatment may be needed to avoid common metabolic effects. Within the class, risperidone has been the most extensively studied and may be considered a first option, provided patients are carefully monitored for increased appetite, weight gain, hyperprolactinemia, sedation, and extrapyramidal symptoms. Aripiprazole, quetiapine, and clozapine are supported by lower-quality evidence, but may be considered when adverse effects limit the use of risperidone.

ADHD often precedes or is comorbid with CD in young patients. Stimulants are the gold standard for the core symptoms of ADHD as well as for aggression in patients with comorbid ADHD and oppositional defiant disorder (ODD) or CD. Results of a meta-analysis indicate that the effects of stimulants on oppositional behavior, conduct problems, and aggression in youth with ADHD, with and without comorbid ODD or CD, are moderate to large. However, few studies evaluated patients with a primary diagnosis of CD.

Limited evidence supports the use of lithium in episodic irritability and impulsive, affective aggression, but it does not appear to have been studied in patients with CD and chronic irritability or predatory aggression. Divalproex has been shown to reduce aggression and temper tantrums in mixed populations of patient with mood lability.

Clonidine, primarily used to treat ADHD, Tourette syndrome, and PTSD, has demonstrated a small effect on conduct problems in young patients with ADHD, with or without comorbid CD or ODD. However the quality of the evidence was very low.

**Recommendations.** In patients with a primary diagnosis of CD without comorbid ADHD, risperidone may be the first treatment option, followed by an alternate second generation antipsychotic if adverse effects are troubling. For patients with comorbid ADHD, evidence supports use of stimulants, followed by add-on risperidone if needed. Patients with CD and comorbid bipolar disorder or suicidality may benefit from lithium. Those with comorbid anxiety disorders and emotional dysregulation without severe aggression, rapid cycling/

mixed mood symptoms may benefit from divalproex. Clonidine may be considered for irritability and/or aggression associated with ADHD, Tourette syndrome, or with PTSD. Because evidence is limited, no guidelines address the duration of treatment. However, the authors suggest that after 1 year of effective behavioral control, discontinuation should be considered.

Pisano S, Masi G: Recommendations for the pharmacological management of irritability and aggression in conduct disorder patients. *Expert Opinion on Pharmacotherapy* 2019; doi 10.1080/14656566.2019.1685498. From AORN Santobono-Pausilipon, Naples; and the Scientific Institute of Child Neurology and Psychiatry, Pisa, Italy. **This review conducted without funding. One study author disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

**Common Drug Trade Names:** aripiprazole—*Abilify*; clonidine—*Catapres*; clozapine—*Clozaril*; quetiapine—*Seroquel*; risperidone—*Risperdal*

## Prenatal Acetaminophen Exposure and ADHD/Autism Risk

Cord blood biomarkers of prenatal acetaminophen exposure were associated with dose-dependent increases in risk of ADHD and autism spectrum disorder (ASD) in childhood. Previous evidence of the association is limited and flawed by methodologic concerns such as recall bias. At present the FDA, the Society for Maternal-Fetal Medicine, and the American Academy of Pediatrics have refrained from attributing causality or making recommendations about maternal use of acetaminophen.

**Methods:** This study was based on data from the ongoing Boston Birth Cohort Study. Children were enrolled at birth, between 1998 and 2018, and were invited to participate in follow-up until age 21 years. More than 3,000 mother–infant pairs were enrolled. Cord blood samples were collected at birth, and maternal plasma metabolites of acetaminophen were measured within 3 days after delivery. The total acetaminophen burden was the sum of the unchanged compound plus metabolites. Exposure was stratified into tertiles. During follow-up, children were classified based on electronic health records as having ADHD alone, ASD alone, ADHD and ASD, other developmental disorders, or neurotypical development.

**Results:** A total of 996 mother–child pairs had sufficient cord blood plasma samples for acetaminophen metabolite assays. During follow-up, 25.8% of children were identified as having ADHD, 6.6% had ASD, 4.2% had both diagnoses, 30.5% had other developmental disorders, and 32.8% were neurotypical. The third (highest) tertile of cord acetaminophen exposure was significantly overrepresented and the lowest tertile was underrepresented among children with the 2 disorders. (See table.) Compared with the first tertile of acetaminophen burden, being in the second and third tertiles was associated with increased risk of ADHD (odds ratios,\* 2.26 and 2.86, respectively) and ASD (odds ratios, 2.14 and 3.62, respectively). Those with other developmental disorders had acetaminophen exposure similar to neurotypical children. All cord acetaminophen metabolites showed a similar relationship to ADHD/ASD risk. Dose-response patterns were identified between both cord unchanged acetaminophen and total acetaminophen burden and risk of ADHD. Adjusting for a wide range of covariates including maternal ADHD, depression, or anxiety and maternal infection did not change the results. Maternal and cord acetaminophen levels were correlated.

Total Acetaminophen Burden in Cord Samples According to Neurodevelopmental Conditions					
	Neurotypical	ADHD	ASD	ADHD and ASD	Other Disorders
First tertile	40.7%	22.2%	16.7%	21.4%	40.1%
Second tertile	32.1%	34.6%	39.4%	40.5%	31.2%
Third tertile	27.2%	43.2%	43.9%	38.1%	28.6%

**Discussion:** By adjusting for a wide range of covariates and directly measuring cord blood acetaminophen burden rather than relying on maternal recall of exposure, this study overcomes important limitations of previous research. It remains unclear whether a specific time window exists when the developing brain is most sensitive to acetaminophen, but animal studies suggest the perinatal period is critical. Other research suggests acetaminophen may be toxic to cortical neurons, inhibits testosterone synthesis, and affects multiple brain functions via inhibition of cyclooxygenase-2.

Ji Y, Azuine R, Zhang Y, Hou W, et al: Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.3259. From Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; and other institutions. **Funded by the U.S. Department of Health and Human Services; and other sources. The authors declared no competing interests.**

\*See Reference Guide.

## Thyroid Screening in Mood/Anxiety Disorders

Although thyroid function tests are routine in children and adolescents at the time of psychiatric hospitalization, the usefulness of thyroid screening in this population is not well known. A study in hospitalized patients with severe mood and anxiety disorders identified factors that could help develop a targeted screening approach.

**Methods:** Electronic medical records were reviewed for 1017 patients consecutively admitted to psychiatric inpatient units at a university medical center over a nearly 5-year period. Patients were included in the analysis if they were aged  $\leq 18$  years, had a mood or anxiety disorder diagnosis, and had a recorded thyroid stimulating hormone (TSH) level. Specific symptoms and other variables suspected to have a relationship with thyroid function were analyzed for associations.

**Results:** TSH was suppressed in 7 patients and elevated in 62. Several factors including recent weight gain, levothyroxine (*Synthroid*) treatment, abnormal uterine bleeding, and a history of thyroid abnormality were found to be associated with a higher likelihood of TSH elevation. In addition, recent treatment with a benzodiazepine (odds ratio,\* 2.29) or lithium (odds ratio, 3.12) was predictive of elevated TSH. Of the patients with elevated TSH levels, 8 had a diagnosed thyroid disease.

**Discussion:** American Academy of Child and Adolescent Psychiatry Practice Parameters recommend consideration of hypothyroidism in the differential diagnosis of pediatric depressive and anxiety disorders. The present observations suggest the cost-effectiveness of thyroid screening in patients with severe mood and anxiety disorders might be improved by limiting it to those who report recent weight gain, abnormal uterine bleeding, treatment with benzodiazepines or lithium, or a history of thyroid disease.

Luft M, Aldrich S, Poweleit E, Prows C, et al: Thyroid function screening in children and adolescents with mood and anxiety disorders. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.18m12626. From the University of Cincinnati; and Cincinnati Children's Hospital Medical Center, OH. **Funded by the NIMH; and the American Academy of Child and Adolescent Psychiatry. Three of 9 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

\*See Reference Guide.

## Varenicline for Adolescent Smoking Cessation

In a placebo-controlled trial, varenicline (*Chantix*), added to smoking cessation counseling, did not improve abstinence rates in adolescents and young adults. This finding adds to the mixed and generally disappointing research on psychological and pharmacological treatments for cigarette smoking in young people. However, secondary study outcomes suggest that varenicline may promote abstinence from tobacco early in treatment.

**Methods:** The trial enrolled treatment-seeking individuals, aged 14–21 years, who smoked daily for  $\geq 6$  months and had failed  $\geq 1$  prior attempt to quit. Because of concerns about possible neuropsychiatric adverse effects of varenicline, those with mood or psychotic disorders, suicidality, homicidality, significant hostility or aggression, or dependence on substances other than nicotine were excluded. All participants were scheduled to attend weekly, individual, skills-based counseling and were instructed to select a quit date. They received 12 weeks of double-blind, randomized treatment with 0.5 or 1 mg varenicline b.i.d. (depending on their weight) or placebo. The primary efficacy outcome was abstinence, defined as  $\geq 7$  days of self-reported abstinence confirmed by urine cotinine measurement, at the end of treatment.

**Results:** A total of 157 patients (mean age, 19 years; 60% male) were randomized to varenicline or placebo. Of these, 90 patients completed the study and 83 contributed long-term follow-up at 26 weeks. At study entry, the mean number of cigarettes smoked per day was 11.5 and the average duration of smoking was  $>4$  years.

Rates of abstinence at the end of treatment were identical in the varenicline and placebo groups at 9%. However, participants who received varenicline were more likely than placebo-treated patients to report 7 consecutive abstinent days at any study visit (40% vs 30%;  $p=0.02$ ; adjusted hazard ratio,\* 1.91). Patients taking varenicline were also more likely to report 7 days of abstinence at the 18-week and 26-week follow-up visit. Adverse events were similar with varenicline and placebo. In particular, neuropsychiatric adverse effects were reported by 32% of patients in the varenicline group and 34% in the placebo group.

**Discussion:** Although abstinence rates in the study were low and did not differ between the treatment groups, secondary findings indicate varenicline may promote abstinence from tobacco early in treatment, which could be continuously reinforced in structured cessation counseling to promote long-term abstinence. In light of preexisting concerns about the drug's neuropsychiatric effects, the study results are reassuring, although the strict exclusion criteria may have reduced the likelihood of these adverse events.

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

Gray K, Baker N, McClure E, Tomko R, et al: Efficacy and safety of varenicline for adolescent smoking cessation: a randomized clinical trial. *JAMA Pediatrics* 2019; doi 10.1001/jamapediatrics.2019.3553. From the Medical University of South Carolina, Charleston. **Funded by the NIH. Two of 7 study authors disclosed financial relationships with commercial sources, including Pfizer, manufacturer of varenicline; the remaining authors declared no relationships with commercial sources.**

\*See Reference Guide.

## Reference Guide

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

**Odds Ratio:** A comparison of the probability of an event in 2 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).

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