

EDITOR'S NOTE

This column reflects our commitment to provide you, the primary care physician, with information that will prove helpful in making informed decisions about the care of your patients who suffer from psychiatric disorders. We will highlight abstracts of high interest to you from our sister publication, *The Journal of Clinical Psychiatry*, and summarize pertinent articles from the general scientific literature. We hope that this section is clinically relevant to your practice and that it will encourage you to expand your horizons.

Menstrual Dysfunction Prior to Onset of Psychiatric Illness Is Reported More Commonly by Women With Bipolar Disorder Than by Women With Unipolar Depression and Healthy Controls

Joffe H, Kim DR, Foris JM, et al.

J Clin Psychiatry 2006;67:297-304

Background: Preliminary reports suggest that menstrual cycle irregularities occur more commonly in women with bipolar disorder and unipolar depression than in the general population. However, it is not always clear whether such abnormalities, reflecting disruption of the hypothalamic-pituitary-gonadal axis, are caused by psychotropic treatments or associated with the disorder per se.

Method: The prevalence of early-onset (within the first 5 postmenarchal years) menstrual cycle dysfunction (menstrual cycle length unpredictable within 10 days or menstrual cycle length < 25 days or > 35 days) occurring before onset of psychiatric illness was compared between subjects with DSM-IV bipolar disorder participating in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) and subjects with DSM-IV unipolar depression or no psychiatric illness participating in the Harvard Study of Moods and Cycles. Data from the Harvard Study of Moods and Cycles were gathered from September 1995 to September 1997, and data from STEP-BD were gathered from November 1999 to May 2001.

Results: Early-onset menstrual cycle dysfunction was reported to have occurred in 101/295 women with bipolar disorder (34.2%), 60/245 women with depression (24.5%), and 134/619 healthy controls (21.7%). Women with bipolar disorder were more likely to have early-onset menstrual cycle dysfunction than healthy controls ($\chi^2 = 16.58$, $p < .0001$) and depressed women ($\chi^2 = 6.08$, $p = .01$), while depressed women were not more likely to have early-onset menstrual cycle dysfunction than healthy controls ($\chi^2 = 0.81$, $p = .37$).

Conclusions: Compared with healthy controls and women with unipolar depression, women with bipolar disorder retrospectively report early-onset menstrual dysfunction more commonly prior to onset of bipolar disorder. Future studies should evaluate potential abnormalities in the hypothalamic-pituitary-gonadal axis that are associated with bipolar disorder.

Remissions in Maternal Depression and Child Psychopathology: A STAR*D-Child Report

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JAMA 2006;295:1389-1398

Background: Children with depressed parents experience high rates of anxiety, disruptive, and depressive disorders; these disorders begin early, often continuing into adulthood, and are impairing. This study sought to establish whether successful treatment with medication of women with major depression correlated with decreased symptoms and diagnoses in their offspring.

Method: Evaluations of children of depressed mothers who were being treated with medication as part of the multicenter Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial conducted (between December 16, 2001 and April 24, 2004) in primary and psychiatric outpatient practices that were broadly representative. The team responsible for assessing children did not participate in the treatment of mothers and was unaware of maternal outcomes. The study is continuing; participants are followed at 3-month intervals. Participants included 151 mother-child pairs in 8 primary care and 11 psychiatric outpatient clinics across 7 regional centers in the United States. Children were from 7 to 17 years old. Child diagnoses were assessed with the Kiddie Schedule for Affective Disorders and Schizophrenia; child symptoms were assessed with the Child Behavior Checklist; child functioning was assessed with the Child Global Assessment Scale in mothers whose depression with treatment remitted with a score of 7 or lower or whose depression did not remit with a score higher than 7 on the Hamilton Rating Scale for Depression.

Results: There was a significant association between remission of maternal depression after 3 months of medication treatment and reductions in the children's diagnoses and symptoms. The rates of diagnoses in children of mothers whose depression remitted decreased 11% overall, while the rates of diagnoses in children of mothers whose depression did not remit increased 8%. Even after

the child's age and sex, and possible confounding factors were controlled for, this rate difference remained statistically significant ($p = .01$). Of the children with a diagnosis at baseline, remission was reported in 33% of those whose mothers' depression remitted compared with only a 12% remission rate among children of mothers whose depression did not remit. In all cases, if children of mothers whose depression remitted after treatment had no baseline diagnosis for depression themselves, they remained free of psychiatric diagnoses at 3 months. On the other hand, 17% of the children whose mothers remained depressed acquired a diagnosis. When child symptoms were used as an outcome, findings were similar. The greater the level of maternal response, the fewer current diagnoses and symptoms in the children; to detect an improvement in the child required a maternal response of at least 50%.

Conclusions: Remission of maternal depression yields positive results for both mothers and their children. Conversely, mothers who remain depressed may increase the rates of their children's disorders. These findings emphasize that aggressive treatment for depressed mothers in primary care or psychiatric clinics is vital and suggest that it is useful to assess the children, particularly children whose mothers remain depressed.

Physical Activity and Sedentary Behavior Patterns Are Associated With Selected Adolescent Health Risk Behaviors

Nelson MC, Gordon-Larsen P
Pediatrics 2006;117:1281-1290

Objective: How physical activity, sedentary behavior, and various adolescent health risk behaviors are associated is largely unknown. This study sought to investigate relationships between physical activity and sedentary behavior patterns and a variety of risk behaviors, including the foremost causes of adolescent morbidity/mortality.

Method: The National Longitudinal Study of Adolescent Health (wave I: 1994-1995; wave II: 1996; $N = 11,957$) collected nationally representative self-reported data. Seven homogeneous groups of adolescents sharing physical activity and sedentary behaviors were identified using previously developed and validated cluster analyses. The relative risk of health risk behaviors, other weekly activities, and self-esteem across the 7 physical activity/sedentary behavior clusters were predicted using Poisson regression, controlling for demographics and socioeconomic status. Adolescent risk behaviors (e.g., truancy, cigarette smoking, sexual intercourse, delinquency), other weekly activities (e.g., work, academic performance, sleep), and self-esteem constituted the main outcome measures.

Results: Compared with high television and video viewers, adolescents in clusters distinguished by skating and video gaming, high overall sports and sports participation with parents, using local recreation centers, strict parental oversight of television, reporting few activities overall, and being active in school were less prone to engage in several risky behaviors, ranging from an adjusted risk ratio (ARR) of 0.42 (outcome: illegal drug use; cluster: strict parental control of television) to 0.88 (outcome: violence; cluster: sports with parents). Active teenagers were less prone to have low self-esteem (e.g., adolescents engaging in sports with parents, $ARR = 0.73$) and more likely to have higher grades (e.g., active in school, $ARR = 1.20$).

Conclusions: Participation in a variety of physical activity-related behaviors, especially those distinguished by high parental sports/exercise involvement, was connected with favorable

adolescent risk profiles. In contrast, adolescents with high television/video viewership were less likely to have positive risk behavior outcomes. Improving opportunities for physical activity and sport may have a positive effect on leading adolescent risk behaviors.

Association of Depression and Anxiety Disorders With Weight Change in a Prospective Community-Based Study of Children Followed up Into Adulthood

Anderson SE, Cohen P, Naumova EN, et al.
Arch Pediatr Adolesc Med 2006;160:285-291

Objective: The investigators sought to examine weight change related to anxiety and depression from childhood to adulthood.

Method: This prospective longitudinal investigation was conducted in Albany and Saratoga Counties, New York. Eight hundred twenty individuals (403 females and 417 males) were evaluated at 4 time points: in 1983 at ages 9 to 18 years ($N = 776$), in 1985 to 1986 at ages 11 to 22 years ($N = 775$), in 1991 to 1994 at ages 17 to 28 years ($N = 776$), and in 2001 to 2003 at ages 28 to 40 years ($N = 661$). A structured diagnostic interview identified anxiety disorders and depression. The main outcome measure was an assessment of weight status developed by the Centers for Disease Control and Prevention, the body mass index z score (BMIz), and association of anxiety and depression with BMIz level and annual change.

Results: In females, anxiety disorders were related to increased weight status, a BMIz of 0.13 (95% CI = 0.01 to 0.25) units higher than females without anxiety disorders. Female depression was related to a gain in BMIz of 0.09 units/year (95% CI = 0.03 to 0.15 units/year), altered by the age at which depression was initially seen, in such a way that early depression onset was related to a higher subsequent BMIz than depression onset at older ages. In males, childhood depression was related to a lower BMIz (-0.46 ; 95% CI = -0.93 to 0.02 units lower at the age of 9 years), but the disparate BMIz paths for males with or without depression converged in adulthood; male anxiety disorders were not substantively related to weight status.

Conclusions: Although anxiety disorders and depression were associated with a higher BMIz in females, these disorders were not associated with a higher BMIz in males. Pending corroboration in additional prospective trials and confirmation of a causal relationship, these results support treating female anxiety and depression as part of comprehensive attempts to prevent obesity.

Association Between Attention-Deficit/Hyperactivity Disorder and Bulimia Nervosa: Analysis of 4 Case-Control Studies

Surman CB, Randall ET, Biederman J
J Clin Psychiatry 2006;67:351-354

Background: Impulsivity is a common feature of attention-deficit/hyperactivity disorder (ADHD), and evidence suggests that impulsivity traits may be an indicator of poor prognosis for individuals with bulimia nervosa. To identify whether there is an association between ADHD and bulimia nervosa, the authors systematically examined data from children and adults with and without ADHD.

Method: We systematically identified rates of bulimia nervosa in individuals with and without ADHD (DSM-III-R crite-

ria) in our 2 large pediatric and 2 large adult samples ($N = 522$ children, 742 adults). Subjects were assessed from the late 1980s to February 1999.

Results: In the 2 samples of adults with and without ADHD, significantly greater rates of bulimia nervosa were identified in women with versus without ADHD (12% vs. 3%, $p < .05$ for 1 sample and 11% vs. 1%, $p < .05$ for the other sample). No significant differences in rates of bulimia nervosa were identified in men or children with ADHD when compared with sex-matched control subjects.

Conclusion: Although preliminary and requiring further confirmation, these findings suggest that ADHD may be associated with bulimia nervosa in some women. If confirmed, this association between bulimia nervosa and ADHD could have important clinical and therapeutic implications.

Open-Label Lithium for the Treatment of Adolescents With Bipolar Depression

Patel NC, DelBello MP, Bryan HS, et al.

J Am Acad Child Adolesc Psychiatry 2006;45:289–297

Objectives: To assess the effectiveness and tolerability of lithium in the treatment of acute depression in adolescents with bipolar disorder.

Method: Open-label lithium 30 mg/kg (twice-daily dosing) was received over a 6-week period by 27 adolescents (12–18 years old) with a depressive episode associated with bipolar disorder type I. Dosages were adjusted to achieve a therapeutic serum level (1.0–1.2 mEq/L). The Children's Depression Rating Scale-Revised (CDRS-R) and the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP) were used to measure effectiveness. Weekly assessments of adverse events were conducted.

Results: The reduction in mean CDRS-R scores from baseline to endpoint was significant (mean [SD] change = -25.5 [20.4]; $p < .001$). The resulting effect size, 1.7, was large. Response ($\geq 50\%$ reduction in CDRS-R score from baseline to endpoint) and remission (CDRS-R score ≤ 28 and CGI-BP Improvement score of 1 or 2) rates were 48% and 30%, respectively. Side effects were generally mild to moderate in severity and included headache (74%), nausea/vomiting (67%), stomach-ache (30%), and abdominal cramps (19%).

Conclusions: Lithium appears to be effective and relatively well-tolerated for the treatment of an acute depressive episode in adolescents with bipolar disorder. These findings need to be replicated with controlled studies of lithium in adolescent bipolar depression.

Outcomes of Late-Life Anxiety Disorders During 32 Weeks of Citalopram Treatment

Blank S, Lenze EJ, Mulsant BH, et al.

J Clin Psychiatry 2006;67:468–472

Background: Anxiety disorders are common in later life, but little is known about the long-term benefits and risks of pharmacotherapy.

Method: Thirty patients aged 60 years and older, with a DSM-IV anxiety disorder, entered a 32-week trial of citalopram. Data gathered at baseline and follow-up included anxiety symptoms using Hamilton Rating Scale for Anxiety (HAM-A) scores, quality of life using the Medical Outcomes Study 36-item Short Form (SF-36), and sleep using the Pittsburgh

Sleep Quality Index (PSQI). Data analysis consisted of mixed-effect repeated measures models of HAM-A scores and pre-post comparison of SF-36 and PSQI scores.

Results: Thirty persons entered treatment; most (27/30) had a primary DSM-IV diagnosis of generalized anxiety disorder (2 had panic disorder; 1 had posttraumatic stress disorder). Three subjects discontinued study medication due to side effects, 5 were terminated because of nonresponse, and 5 dropped out of the study for other reasons; thus, 17 subjects (57%) completed 32 weeks of treatment. Subjects' HAM-A scores improved significantly, with continuing improvements up until about 20 weeks of treatment. On the basis of a criterion of reduction in HAM-A to < 10 during the trial, 60% (18/30) of subjects were responders. Those who completed the 32-week trial had significant improvements in sleep and quality of life—including social functioning, vitality, mental health, and role difficulties due to emotional problems.

Conclusions: In this 32-week study of citalopram for elderly persons with anxiety disorders, 60% responded. Those who received a full course of treatment experienced significant improvements in quality of life and sleep quality.

A Double-Blind, Multicenter, Parallel-Group Study of Paroxetine, Desipramine, or Placebo in Breast Cancer Patients (stages I, II, III, and IV) With Major Depression

Musselman DL, Somerset WI, Guo Y, et al.

J Clin Psychiatry 2006;67:288–296

Objective: This study compared the efficacy and safety of paroxetine and desipramine with those of placebo in the treatment of depressive disorders in adult women with breast cancer, stages I–IV.

Method: In a double-blind, placebo-controlled study, 35 female outpatients with breast cancer and DSM-III-R major depression or adjustment disorder with depressed mood were randomly assigned to treatment with paroxetine ($N = 13$), desipramine ($N = 11$), or placebo ($N = 11$) for 6 weeks. Primary efficacy was assessed by change from baseline in score on the 21-item Hamilton Rating Scale for Depression (HAM-D), and the secondary outcome measure was change from baseline in the Clinical Global Impressions-Severity of Illness scale (CGI-S) score.

Results: Mean changes in the total HAM-D and CGI-S scores from baseline to 6-week endpoint for the paroxetine and desipramine groups were not significantly different than those for the placebo-treated group. An unusually high rate of response (defined as $\geq 50\%$ improvement in the HAM-D score) in the placebo group was observed (55% [$N = 6$]); adverse events precipitated patient discontinuation in the active treatment groups (9% [$N = 1$] for desipramine, 15% [$N = 2$] for paroxetine) similar to that in the placebo-treated patients (18% [$N = 2$]). Improvement on symptom dimensions within the HAM-D and Hamilton Rating Scale for Anxiety (depressive, anxiety, cognitive, neurovegetative, or somatic) was also similar between groups.

Conclusion: The small number of women in this study most likely contributed to the lack of observed differences in efficacy observed during the 6 weeks of treatment. Randomized, placebo-controlled trials of adequate power seeking to determine efficacy of antidepressants in the United States for the treatment of women with breast cancer and comorbid depression remain of paramount importance.

Analysis of Electrocardiographic Data Following Use of Paroxetine in Pediatric Depression and Obsessive-Compulsive Disorder

Krulewicz S, Carpenter DJ, Fong R, et al.

J Am Acad Child Adolesc Psychiatry 2006;45:422-430

Objective: To investigate the cardiovascular effects of paroxetine in pediatric patients. Data were retrieved from three 8- to 10-week, randomized, placebo-controlled, double-blind trials of paroxetine in pediatric patients with major depressive disorder or obsessive-compulsive disorder.

Method: Electrocardiograms (ECGs) were collected from 63 study sites in the United States and Canada in this retrospective study of three 8- to 10-week, randomized, placebo-controlled, double-blind trials of paroxetine in pediatric patients with major depressive disorder or obsessive-compulsive disorder. Inclusion was restricted to patients aged 7 to 18 years taking paroxetine 10 to 50 mg/day with at least 1 screening and 1 on-treatment ECG. ECGs were evaluated for heart rate, QT interval corrected using Bazett's formula (QTcB) and Fridericia's formula (QTcF), at screening and during therapy. PR, R-R, and QRS intervals and the maximum change in QTcB and QTcF from screening to endpoint were assessed. Clinically significant thresholds were defined a priori.

Results: Investigators evaluated a total of 1451 ECGs from 449 patients receiving placebo (N = 207), paroxetine (N = 200), or imipramine (N = 42). Neither QTcB nor QTcF or any ECG parameters were significantly elevated in individuals receiving paroxetine compared with those receiving placebo. Treatment with imipramine significantly increased heart rate and QTcB, R-R, and QRS intervals compared with either paroxetine or placebo.

Conclusions: In medically healthy pediatric patients, paroxetine (10-50 mg/day) is unlikely to be associated with significant ECG changes.

St. John's Wort (*Hypericum perforatum*) and Breastfeeding: Plasma and Breast Milk Concentrations of Hyperforin for 5 Mothers and 2 Infants

Klier CM, Schmid-Siegel B, Schafer MR, et al.

J Clin Psychiatry 2006;67:305-309

Background: Herbal preparations for depression, such as St. John's wort, are often preferred over pharmaceutical preparations by mothers and midwives after childbirth because these preparations are available to patients as over-the-counter "natural" treatments and are popularly assumed to be safe. The only existing report on St. John's wort excretion into human milk showed that only 1 active component (hyperforin) was detectable in breast milk but was not detectable in the infants' plasma. Another report found more cases of minor problems in infants breast-fed by women taking St. John's wort. However, significance was reached only in comparison with disease-matched women ($p < .01$), not healthy controls ($p = .20$).

Method: Five mothers who were taking 300 mg of St. John's wort 3 times daily (LI 160 [Jarsin], Lichtwer Pharma GmbH; Berlin, Germany) and their breastfed infants were assessed. Thirty-six breast milk samples (foremilk and hindmilk collected during an 18-hour period) and 5 mothers' and 2 infants' plasma samples were analyzed for hyperforin levels by tandem mass spectrometry (LC/MS/MS; limit of quantification = 0.1 ng/mL). Data were gathered from January 2001 to February 2002.

Results: Hyperforin is excreted into breast milk at low levels. However, the compound was at the limit of quantification in the 2 infants' plasma samples (0.1 ng/mL). Milk/plasma ratios ranged from 0.04 to 0.13. The relative infant doses of 0.9% to 2.5% indicate that infant exposure to hyperforin through milk is comparable to levels reported in most studies assessing antidepressants or neuroleptics. No side effects were seen in the mothers or infants.

Conclusion: These results add to the evidence of the relative safety of St. John's wort while breast-feeding found in previous observational studies.

Relationship of Family Environment and Parental Psychiatric Diagnosis to Impairment in ADHD

Pressman LJ, Loo SK, Carpenter EM, et al.

J Am Acad Child Adolesc Psychiatry 2006;45:346-354

Objective: Family environmental factors and the presence or absence of attention-deficit/hyperactivity disorder (ADHD) in parents have previously been associated with variability in ADHD. The present study assessed connections among family environment, parental psychiatric status, and child impairment in a cohort of ADHD-affected sibling pairs (ASPs) aged 5 to 18 years.

Method: Parents in 220 ASP families completed the Family Environment Scale, a measure of family functioning. Clinical ratings of global functioning and maternal ratings of behavior assessed children's impairment.

Results: Families were rated as higher in conflict and lower in achievement and organization by parents of children with ADHD than by parents of children in normative samples. High family conflict was significantly associated with impairment in ADHD, with ASPs accounting for approximately 40% of the sibling similarity in impairment. Although there was no significant direct link between parental psychiatric diagnosis and sibling impairment, a significant indirect link to impairment was mediated by family conflict. In spite of the comparable mean impairment scores for older and younger ADHD siblings, direct associations with parental diagnosis depended on birth order of the ASP members.

Conclusions: The researchers found strong links between impairment in children with ADHD and family environment. It is possible that different processes and mechanisms contribute to impairment in different children in the same family.