Adjunctive Aspirin in Schizophrenia

When added to a partially effective antipsychotic, aspirin resulted in marked improvement in an adolescent with schizophrenia.

After showing intermittent signs of psychosis for about 1 year, a 13-year-old boy was admitted to an inpatient psychiatric unit for increasingly bizarre behavior. The patient was experiencing typical symptoms of schizophrenia: paranoid delusions; hallucinations; fear and confusion; illogical thoughts; flat affect; and withdrawal from others. His Positive and Negative Syndrome Scale (PANSS) score was 79 at the time of admission. Aripiprazole was started and then titrated to 20 mg/day. He showed modest improvement, but after 3 weeks, he still had prominent negative symptoms and a PANSS score of 59.

Given the lack of progress, the patient was started on adjunctive aspirin at 325 mg b.i.d. Within 2 days, his hallucinations lessened, he appeared less distracted by internal stimuli, and he spoke more fluently, showed facial expression, and began to interact with others on the unit. His PANSS score decreased over 2 days to 45, with improvement in both positive and negative subscales. This allowed discharge several days later to intensive in-home care.

Dopamine dysfunction is considered the central defect in schizophrenia, but interest is growing in the contributory role of inflammation and immune activation. Clinical trials of aspirin, NSAIDs, and other drugs with antiinflammatory properties have had promising results in adults. In previous adult studies, the NSAID celecoxib had more pronounced effects in patients with shorter disease duration. Possibly NSAIDs are most effective when used shortly after the onset of psychosis, which may provide an advantage in children and adolescents.


Drug Trade Names: aripiprazole—Abilify; celecoxib—Celebrex
Aripiprazole for Tourette Syndrome

In a manufacturer-sponsored, multicenter, randomized, placebo-controlled trial, aripiprazole (Abilify) was both safe and effective in children and adolescents with Tourette syndrome.

Methods: Study participants (n=60), aged 6–18 years, had a diagnosis of Tourette syndrome or chronic vocal or motor tic disorder, according to DSM-IV criteria. Patients were required to have a baseline total tic score of ≥22 on the Korean version of the Yale Global Tic Severity Scale (YGTSS), indicating moderate severity. After random assignment, aripiprazole was started at 2 mg/day and titrated to a maximum of 20 mg/day. Patients were evaluated for a dose increase every 2 weeks and advanced to the next-higher dose if they tolerated the present dose but had a Clinical Global Impression–Improvement* rating of ≥3. The final outcome assessment was conducted at week 10, and the primary efficacy measure was change from baseline in the YGTSS.

Results: Both the aripiprazole and placebo groups showed declines in YGTSS total score during treatment, but the decline was larger in the aripiprazole group (−15 vs. −9.6 points; p=0.0196). Mean changes in the phonic tic subscale of the YGTSS also favored aripiprazole (p=0.043), but both groups had similar changes in the motor tic score. Tic scores decreased in a linear fashion over the 10 weeks in both groups, with statistically significant differences in favor of aripiprazole at weeks 2, 6, and 10. Mean YGTSS total scores decreased by 53% overall with aripiprazole and by 33% with placebo (p=0.0077).

Aripiprazole was associated with mild-to-moderate adverse effects that did not result in treatment discontinuation. Body weight increased by a mean of about 3.5 lbs with aripiprazole and 0.4 lb with placebo, a significantly different change (p=0.0055).

Discussion: Atypical antipsychotics are often used in the treatment of Tourette syndrome, but they have not shown superiority to conventional neuroleptics and lack FDA approval for this indication. Aripiprazole may have unique efficacy in this disorder because its dopamine partial agonist activity may counteract the tonic dysregulation of dopamine signaling that has been proposed to underlie Tourette syndrome.

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


*See Reference Guide.

Long-Term Effects of Depression-Prevention Therapy

A group cognitive-behavioral prevention (CBP) program appeared to protect young patients from recurrent depressive episodes.1

Methods: This randomized trial compared cognitive therapy to usual care in adolescents, aged 13–17 years, treated at 4 geographically diverse U.S. sites. Participants had a parent or caretaker with a history of depression and were themselves experiencing subsyndromal depressive symptoms or had a history of depression, now in remission. The experimental treatment was the Coping with Depression Course for Adolescents, modified for prevention. Treatment was administered in 8 weekly, 90-minute, mixed-gender group sessions and 6 monthly continuation sessions. Time to onset of depression was the primary study outcome. The 9-month results from this study were previously reported;2 additional assessments were carried out 1 and 2 years after the end of continuation treatment (21 and 33 months post-baseline).
Results: Of the sample of 316 adolescents, 268 (85%) completed the 33-month assessment. Retention rates varied among sites, from 62% to 100%. The analysis was based on all randomized patients.

At the 33-month assessment, the CBP treatment was associated with a significantly lower rate of depression than usual care (37% vs. 48%; p=0.04; number needed to treat* [NNT], 10). Prevention appeared to be effective only in adolescents whose parents were not experiencing depression at the start of CBP (about half of the sample). In these adolescents, depression occurred in 32% of those who underwent CBP and in 52% of those treated with usual care (p=0.01; NNT, 6). Depression had onset in about 42% of young people whose parents were experiencing depression at baseline, regardless of treatment.

The effect of CBP was superior to usual care at 2 of the 4 sites, did not differ at 1 site, and was inferior at 1 site. The analysis identified an interaction between parental depression and treatment site. In the 2 sites that had minimal patient attrition (0% and 3%), CBP was consistently superior to usual care, regardless of parent depression. In the sites with higher attrition (20% and 40%), CBP was not superior to usual care.

Discussion: Parental depression may have reduced the efficacy of CBP by interfering with adolescents’ participation, as a result of shared genetic vulnerability, or via disruptive parenting or greater exposure to stressful life events. It may be preferable to treat depression in parents first or concurrently with adolescent CBP. The differential attrition rates between centers may partially account for the heterogeneity of results and may also reflect different rates of parental depression.

1Beardslee W, Brent D, Weersing R, Clarke G, et al: Prevention of depression in at-risk adolescents: longer-term effects. JAMA Psychiatry 2013:70 (November):1161–1170. From Boston Children’s Hospital, MA; and other institutions. Funded by the NIMH; and other sources. One author disclosed a relationship with a commercial source; the remaining authors declared no conflicts of interest.


*See Reference Guide.

Therapy for Posttraumatic Symptoms in Adolescents

In a small group of adolescents exposed to trauma, participation in acceptance and commitment therapy (ACT) reduced symptoms of posttraumatic stress.1

Background: The majority of young people exposed to traumatic events never go on to meet criteria for posttraumatic stress disorder (PTSD), but many, like those in this study, develop subthreshold posttraumatic stress symptoms and functional impairment. ACT, the treatment investigated in the present study, is an acceptance- and mindfulness-based intervention that targets cognitive and emotional avoidance.

Methods: Study participants (n=7), aged 12–17 years, were experiencing significant distress and/or functional interference following a traumatic event (e.g., physical or sexual abuse, natural disaster, death of a caregiver). Community-dwelling adolescents were recruited using multiple methods, including advertising and soliciting referrals from medical and mental health clinicians. Recruitment was also extended to a residential treatment facility for girls with eating disorders. Adolescents with comorbid depression or anxiety were not excluded. Participants completed daily subjective ratings of frequency, distress, and/or interference in 5 different areas: avoidance; reexperiencing; arousal; distress from posttraumatic stress symptoms; and interference with daily functioning. ACT treatment consisted of 10 manualized sessions with the goals of reducing experiential avoidance; developing strategies to respond to
Results: The community sample was 4 adolescents (2 boys), and the residential group was 3 girls from the eating-disorders facility. The community sample had a 69% reduction from baseline in posttraumatic stress symptom scores immediately after treatment and a 68% reduction at follow-up (3 months after the final session). One patient discontinued treatment after the third session because she was feeling better. Her symptom ratings were much improved but at the end of treatment were still above the clinical threshold for PTSD, based on the Clinician Administered PTSD Scale for Children and Adolescents. In the inpatient sample, average symptom reductions were 81% posttreatment and 84% at follow-up. By 3 months, all 7 patients were below the clinical threshold for posttraumatic stress symptom severity. Positive changes in avoidance and psychological flexibility were observed in 6 patients, according to the Avoidance and Fusion Questionnaire for Youth. All patients reported that they found the treatment acceptable.

Discussion: Currently cognitive behavioral therapy (CBT) has the most research support for treating childhood and adolescent posttraumatic stress, but additional options are needed. The fundamental premise of cognitive behavioral therapy (CBT) is that by affecting emotions and behavior, cognitions reinforce emotional disorders. ACT is related to traditional CBT and shares many techniques and strategies. However, ACT differs fundamentally from CBT in that it views cognition as a form of behavior and does not attempt to refute maladaptive cognitions. Patients are taught to increase their psychological flexibility using a set of techniques including acceptance of their negative emotions, cognitive defusion, being present, and committed action. Despite this fundamental difference, ACT and CBT share many techniques, including exposure exercises, problem-solving, role playing, and homework.

New Conduct Disorder Scale

Results of a study undertaken in part to validate the new and relatively brief Delinquent Activities Scale (DAS) indicate that peer groups are a strong influence in the development of conduct disorder and that parental problems are less influential.

Background: Several structured interviews exist to confirm the diagnosis of conduct disorder, including the Diagnostic Interview Schedule for Children, the Diagnostic Interview for Children and Adolescents, and the Schedule of Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime. However, these instruments are often lengthy and require an experienced clinician.

Methods: The DAS, a copy of which is available at http://www.midss.org/content/delinquent-activities-scale-das, is a 37-item structured interview used to assess antisocial behavior, including frequency, age of onset, and whether alcohol or drugs were involved in the behavior. The DAS was administered to 190 adolescents upon intake to a correctional facility and again about 3 months after discharge. Symptom severity, according to the DAS, was calculated using symptom counts. To determine whether severity was associated with parent problems, the following were analyzed: parent problems arising from substance use, peers with substance use or arrest records, and the participant’s own substance use.
**Results:** Study participants had a mean age of 17 years, and most (86%) were male. Severity of conduct disorder was associated with 2 of 10 parent factors assessed: father’s problem with work (p=0.02) and mother’s problem with the law (p=0.03). Effect sizes for these relationships were small. In contrast, conduct disorder severity was robustly associated with negative peer variables: friends’ substance use (p=0.003) and having friends who had been arrested (p=0.005). Severity was also associated with increasing numbers of friends using substances and with past arrests. Child onset of conduct disorder was, unexpectedly, not associated with problematic peers or with age at first alcohol use.

Concurrent incremental validity of the DAS was tested to determine whether it added anything to predictions of the intensity of alcohol and marijuana use based on other factors—i.e., age, race, peer influences, and age of first use. The incremental contribution of conduct disorder severity to these predictions was either nonsignificant or statistically significant but small.

**Discussion:** The conduct disorder scale derived from the DAS appears reliable over time but made a small contribution to incremental concurrent validity. This is a rigorous test that does not appear to have been applied to other diagnostic instruments for conduct disorder, the authors point out.

Reavy R, Stein L, Quina K, Paiva A: Assessing conduct disorder: a new measurement approach. *Journal of Correctional Health Care* 2013; doi 10.1177/1078345813505448. From the University of Rhode Island, Kingston; and other institutions. Funded by the National Institute on Drug Abuse; and the National Institute on Alcoholism and Alcohol Abuse. The authors declared no competing interests.

### Maternal Smoking and Bipolar Disorder

An association between maternal smoking during pregnancy and externalizing behaviors in offspring has been well documented. According to results of a nested case-control study, risk of bipolar disorder is also increased in the adult offspring of mothers who smoke during pregnancy.¹

**Methods:** Study participants were members of a California birth cohort, born between 1959 and 1966, whose mothers received prenatal care from a single source. Members of the cohort were screened for possible bipolar I, bipolar II, or bipolar NOS disorder, using a combination of electronic record screening and mailed questionnaires. From these candidates, in-person diagnostic interviews identified 79 individuals with bipolar disorder. Each case patient was matched with up to 8 controls for age, gender, and other factors. Maternal smoking was identified by a questionnaire administered during prenatal care.

**Results:** Offspring exposed to maternal smoking during pregnancy had a nearly 2-fold increased risk of bipolar disorder (unadjusted odds ratio,* 1.82; p=0.01). This risk remained essentially unchanged after adjustment for birth weight, maternal psychopathology, and maternal alcohol or caffeine use during pregnancy (odds ratio, 2.01; p=0.01). Of all the factors included in a multivariate analysis, only maternal smoking affected the occurrence of bipolar disorder in the offspring. Among offspring with bipolar disorder and no psychotic features, maternal smoking was associated with a more than 2-fold increased risk for the disorder.

**Discussion:** Much of the psychopathology already associated with prenatal tobacco exposure—ADHD and oppositional defiant, conduct, and substance use disorders—has externalizing characteristics. Although not classified on the externalizing spectrum, bipolar disorder has some characteristics in common, including inattention, irritability, loss of self-control, and a proclivity to substance use. The association of tobacco exposure with only nonpsychotic bipolar disorder suggests outcomes of exposure are related to externalizing rather than psychosis-related disorders. Although the association between maternal smoking and offspring bipolar disorder was clear, causality cannot be assumed.
Editorial: According to an accompanying editorial, the study results have several possible interpretations. Maternal smoking may directly affect neurodevelopment, and the association with bipolar disorder and externalizing disorders may reflect the neurotoxic effects of nicotine and carbon monoxide, which readily cross the placenta. Alternatively, the association may reflect a common exposure of the mother and offspring to genetic influences and environmental stressors. Continuing to smoke during pregnancy may be related to antisocial traits, risk-taking, and reduced attention to one’s well-being. Maternal smoking may also be related to adverse child-rearing practices, family stress and conflict, and socioeconomic disadvantage. It is likely that the biological actions of smoking in pregnancy only explain some of the associated risk, beyond genetic and environmental influences.


*See Reference Guide.*

**Reference Guide**

Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

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.

Number Needed to Treat (NNT): Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value the less effective is the treatment.

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.

In 2012, the annual index (previously included in the December issue) was made available as a printable document on our web site and through email. Feedback from our valued subscribers let us know you preferred it that way! As a result, the 2013 index will be distributed the same way.

If you currently receive issues by email, you will automatically receive the index that way. If you do not currently receive issues by email but would like to receive the index, send an email to Krista@alertpubs.com and put “Index” in the subject line.