

## Atypical Antipsychotic Adherence in Adolescents

Atypical antipsychotics are now used for the treatment of mood disorders in a wide variety of patients. While several studies have focused on the safety and efficacy of antipsychotics in adults, data are lacking regarding adolescent patients. Additionally, adherence rates and predictive factors that are associated with adherence have not been thoroughly investigated. This study, by David L. Pogge, PhD, Four Winds Hospital, Katonah, NY, and colleagues, evaluated 156 adolescent patients with mood disorders 120 days following discharge from their first inpatient admission.

All patients were taking either aripiprazole (n=96) or quetiapine (n=60) at the time of hospital discharge and were evaluated prior to atypical antipsychotic therapy. Of the 156 adolescent participants, 70 had depression spectrum disorders, 62 had conduct-related disorders, and 24 had bipolar spectrum disorders (as determined by consensus procedure in tandem with K-SADS structured diagnostic assessment). Participants were rated for severity of mood symptoms at baseline (hospital admission), 30 days postdischarge, and 120 days postdischarge using the Hamilton Rating Scale for Depression (HAM-D-17 item) and the Young Mania Rating Scale (YMRS). Assessments were performed via telephone interview at Day 30 postdischarge and in person at 120 days postdischarge. Patients were then stratified according to adherence. Adherence categories included: adherent (taking antipsychotic treatment as prescribed), discontinued (cessation of antipsychotic treatment at the advice of their physician, parent, or guardian), nonadherent (cessation of antipsychotic treatment against medical advice), and lost to contact prior to Day 30.

Adherence rates were similar for both quetiapine and aripiprazole (53% vs 69% at Day 30 and 48% vs 64% at Day 120, respectively). In adherent patients, HAM-D and YMRS scores improved from pretreatment baseline to follow-up at 120 days ( $p < 0.05$  for both quetiapine and aripiprazole). In those who took quetiapine, higher baseline HAM-D scores were associated with better adherence rates. The average dose of quetiapine in adherent patients was 240 mg. However, adherence predictability did not appear to be associated with aripiprazole and baseline HAM-D score. While low discharge doses of quetiapine (average dose of 83 mg) were found to be associated with nonadherence and discontinuation during the follow-up course of the study, no correlation was observed concerning discharge dose of aripiprazole and poor adherence. It is important to note

that though the dosing range for aripiprazole was limited, there was a large variation in the quetiapine doses.

Overall adherence rates for both groups were favorable, demonstrating long-term benefits from atypical antipsychotic therapy in adolescents. However, dose may be an important factor to consider, particularly related to quetiapine therapy. Adherence to aripiprazole therapy did not appear to have the same associated dose effect that was observed with quetiapine.

There are two critical points to consider with regard to this study. First, the dose variation among those who were taking quetiapine may have influenced these findings. The average low dose of quetiapine was 83 mg in nonadherent patients, while the average higher dose of quetiapine was 240 mg in adherent patients. Second, many adolescents may progress from unipolar depression to bipolar disorder over time, and this study is limited by heterogeneous diagnoses.

## Conduct Disorder and ADHD: Predictors for Substance Abuse

ADHD and associated comorbidities are known to be risk factors for substance abuse in adolescence and young adulthood, but few studies have examined the early childhood risk factors that may predispose to this behavior. In a 10-year follow-up of children with attention deficit hyperactivity disorder (ADHD), the occurrence of substance use disorder (SUD) was increased compared with controls, especially among ADHD youth with early conduct disorder, according to a study from by Timothy E. Wilens, MD, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

“We hypothesized that early delinquency and academic or cognitive dysfunction will predict later SUD in two cohorts of ADHD children, followed for an average of 10 years. We examined early predictors for later SUD,” said Dr. Wilens.

The study compared 257 youths with ADHD to 225 youths without ADHD. All subjects were aged 6 to 17 years at baseline and were followed for approximately 10 years. Study subjects were assessed in a blinded manner using DSM-IV Schedule for Affective Disorders and Schizophrenia for School-Aged Children, epidemiological edition (KSADS-E), or Structured Clinical Interview for DSM Disorders (SCID), cognitive measures, Family and Environmental Scale (FES), and Social Adjustment Inventory for Children and Adolescents (SAICA) rating scales. Psychopathology and SUD were determined by structured interview.

At baseline, the subjects had a mean age of 11 years, and 50% of the study population was male. Most were Caucasian

from middle-class families. The subjects and controls were similar except that ADHD subjects were significantly more likely to have a parental history of alcohol use disorders ( $p < 0.001$ ) and drug use disorders ( $p = 0.003$ ).

Investigators found that children with ADHD were 1.5 times more likely to develop a SUD compared with controls. Within ADHD, comorbid oppositional defiant disorder and conduct disorder were significant predictors of any SUD, after adjusting for gender (hazard ratio [HR], 2.31;  $p < 0.001$ ) and parental history of SUD (HR, 3.0;  $p < 0.001$ ).

Within the population of ADHD youths who developed drug use disorders, comorbid major depressive disorder was a further significant predictor, essentially doubling the risk ( $p = 0.006$ ). Analysis showed that boys who received extra help in school were approximately half as likely to develop a SUD ( $p = 0.02$ ).

“In general, gender did not predict risk for SUD, and we found no significant associations between baseline cognitive or academic dysfunction and later SUD in our ADHD youth,” Dr. Wilens said. “No significant results were found for social or family environment factors, cognitive factors, or any school functioning factors.”

“Dr. Wilens and colleagues showed that there are children with ADHD that are at risk for substance abuse, but most of them have a diagnosis of conduct disorder, which translates into juvenile delinquency later. Many ADHD children want to be good. For the child with conduct disorder, ‘being good’ is not a priority. This work says that ADHD plus conduct disorder equals a very serious problem,” commented R. Scott Benson, MD, APA Council on Communications.

The study suggests that the vast majority of ADHD children will not abuse drugs later, but if a child has more severe, oppositional behavior, that child may be at risk of developing serious substance abuse issues. The challenge for psychiatrists is to find ways to treat these comorbidities.

## Prescription Opioid Dependence: Relapses Associated with Shorter Treatment Course

The National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study found that patients who tapered off prescription opioids using buprenorphine during a 9-month period, whether initially or after a period of improvement, almost universally relapsed. “There has been virtually no research on the treatment of persons dependent on prescription opioids, in spite of the major increase in

prescription opioid abuse and in the numbers of persons entering treatment for addiction to prescription opioids,” said Roger D. Weiss, MD, Harvard Medical School, Boston, and McLean Hospital, Belmont, MA.

The study, which is the largest treatment study ever conducted for prescription opioid dependence (POD), sought to determine the optimal length of pharmacotherapy and the value of intense counseling.

The study investigated whether adding intense counseling to buprenorphine-naloxone plus standard medical management improved patient outcomes, what duration of buprenorphine is best, and whether chronic pain influenced outcomes.

The study enrolled 653 persons at 10 sites with POD and offered them standard medical management, which included buprenorphine (12-16 mg maximum, adjusted for addiction), an initial 1-hour visit, and weekly 20-minute sessions with a physician who counseled them and monitored for drug side effects. Half of the group remained in this standard medical management (SMM) arm while half received enhanced medical management (EMM) that included twice-weekly 60-minute individualized drug counseling sessions that were focused on interpersonal issues, coping with triggers, and high-risk situations.

Patients were evaluated after periods of individualized buprenorphine tapering and maintenance and were assessed for abstinence from opioids at various periods.

All patients had a DSM-IV diagnosis of opioid dependence and had used opioids for at least 20 of the past 30 days. The average subject was 33 years old and had been using opioids for 4.5 years, including sustained-release oxycodone (35%), hydrocodone (32%), immediate-release oxycodone (19%), methadone (6%), and others (8%). For 70% of subjects, this was the first treatment for opioid dependence.

Patients reported current chronic pain (42%), a history of heroin use (23%), alcohol abuse (60%) or dependence (27%), cannabis abuse (47%) or dependence (15%), and cocaine abuse (32%) or dependence (18%).

Treatment success was defined as  $\leq 4$  days of opioid use per month, no positive urine screens for opioids for 2 consecutive weeks, no other formal substance abuse treatment, and no opioid injections.

Phase 1 included 1 month of tapering and 2 months of stabilization. At the end of this period, few patients were successfully treated, and enhanced management did not influence the results. In the SMM group, only 7% met the criteria for success, as did just 6% of the EMM group ( $p = 0.45$ ). “Nearly all patients relapsed after a 4-week taper,” Dr. Weiss reported.