Treating Substance Abuse in Conduct Disorder

Of several effective interventions, multisystemic therapy (MST) has the most compelling evidence for treatment of substance use disorders in adolescents with conduct disorders, according to a systematic review.

Substance abuse treatments in adolescents vary widely in technique, intensity, setting, and duration. Conduct and substance use disorders are the most prevalent comorbid psychiatric disorders in adolescence, and the conduct problems often lead to poorer outcomes of substance abuse treatment. This patient population is difficult to study, underserved, and under-researched. Randomized clinical trials comparing the treatments have not been conducted to date.

The authors identified peer-reviewed research articles, published since 1979, describing the treatment of substance use problems in youths, aged 8–20 years, with conduct disorder or oppositional defiant disorder. After careful review, they found that while the major forms of therapy—MST; cognitive behavioral therapy (CBT); 12-step programs; psychoeducation; and motivational interviewing—were all effective, MST appears to be the optimal treatment.

Both CBT and 12-step programs are effective, however for both, effectiveness is dependent on treatment retention. CBT is more effective in older males than in girls or younger males, but it is equally effective in association with race. This is important because many substance abusing adolescents with conduct problems are minority youths. Twelve-step programs could benefit from groups comprised entirely of adolescents, rather than mixed-age groups.

There has been little research on psychoeducation, in part because it has no established theoretical framework. Its effects are positive, but not as robust as the other treatments. Psychoeducation may be especially effective in residential treatment settings. Motivational interviewing is a brief, resource-efficient approach that may work especially well when it is front-loaded to other treatments, especially CBT.
The effects of MST in reducing substance use and antisocial behavior in adolescents with conduct problems are supported by 20 years of research. MST is a family-oriented treatment that aims to keep the adolescent within the family’s custodial care by improving parental monitoring and supervision; enhancing social supports; restricting access to deviant peer groups; treating parental substance abuse and other psychopathology; and improving parent-child interactions. MST also has economic advantages because it reduces relapses, residential treatment, use of wilderness programs, and use of the juvenile justice system. MST is associated with not only reduced substance use, but improved relationships with siblings and decreased substance use among siblings. MST has no unique curative factors but benefits from being well-established and standardized, with a high level of therapist training and supervision, treatment fidelity, methodologic rigor, and the ability to address numerous contributing factors.

Spas J, Ramsey S, Paiva A, Stein L: All might have won, but not all have the prize: optimal treatment for substance abuse among adolescents with conduct problems. *Substance Abuse: Research and Treatment* 2012;6:141–155. From the Warren Alpert Medical School of Brown University, Providence, RI; and other institutions. This review was conducted without external funding. The authors disclosed no conflicts of interest.

**Antipsychotics and Rhabdomyolysis Risk**

Rhabdomyolysis is a rare and relatively undocumented adverse effect of antipsychotic medications that is caused by skeletal muscle destruction that results in leakage of muscle constituents into plasma. Most cases occur in conjunction with neuroleptic malignant syndrome (NMS), but antipsychotic-associated rhabdomyolysis can also occur in the absence of this syndrome. This potentially serious adverse effect is of concern given the increasing use of antipsychotics in children and adolescents.

A literature review identified published case reports of antipsychotic-associated rhabdomyolysis in young patients. A systematic search of the World Health Organization’s VigiBase database, which contains postmarketing adverse event data from 97 countries, identified additional cases. A total of 26 cases were reported in patients aged ≤17 years, of which 20 occurred in the absence of NMS. Each case underwent detailed analysis.

Rhabdomyolysis was disproportionately reported for olanzapine (n=11) but occurred with a wide range of agents including risperidone (n=5), haloperidol (n=4), and several other second-generation drugs. For 14 of the 20 non-NMS-related cases, the antipsychotic was reported as the only suspected causal medication. In 6 reports (including 3 with NMS), additional drugs may have contributed to the syndrome, including mood-stabilizing anticonvulsants or lithium, and antidepressants.

The timing of rhabdomyolysis onset relative to antipsychotic initiation was determined in 16 patients and ranged from 2 days to 1.5 years. Most cases occurred within 2 days of IM antipsychotic injections, within 3–7 days of a dose increase or addition of a second antipsychotic, or within a few weeks to 2 months in patients with an underlying risk factor. One case occurred after 1.5 years of apparently stable therapy. Abdominal cramps and general muscle pain were the most common symptoms in the week preceding rhabdomyolysis diagnosis. Additional risk factors were reported for 9 patients and included: strenuous physical activity; seizures; IM drug administration; diabetic ketoacidosis; alcohol use; hyperthermia; and possible infection.

Following rhabdomyolysis diagnosis, the antipsychotic was withdrawn in all 26 patients; 21 of the patients recovered. One patient had a leg amputation, and 1 died of multisystem failure. Although information is limited, it appears that the remaining patients had continued renal problems and/or had not recovered at the time of reporting.
It is unclear from the available data whether the apparently higher incidence of rhabdomyolysis with olanzapine is a true increase or if reporting bias, following a few early case reports, could be a factor. The rarity of rhabdomyolysis and its nonspecific early symptoms might contribute to under-reporting. Monitoring of young patients should be intensified following a new prescription, dose increase, or switch to a new antipsychotic, as well as after exposure to known risk factors for rhabdomyolysis.


**Drug Trade Names**: haloperidol—**Haldol**; olanzapine—**Zyprexa**; risperidone—**Risperdal**

### Intrasinal Ketamine for Bipolar Disorder

In a preliminary study, intranasal ketamine was strikingly effective in a subgroup of children and adolescents with bipolar disorder who exhibited a fear-of-harm phenotype (BD-FOH). This severe form of the disorder, refractory to other treatments, continued to respond to repeated administration of ketamine every few days.

**Background**: The fear-of-harm phenotype is a variant of bipolar disorder with additional features not listed among the DSM-IV bipolar criteria, including fear of aggression, separation anxiety, sleep/arousal disorders, and nightmares. Some symptoms appear to be consistent with reactive aggression due to perceived threats. In addition, patients may have dysregulation of body temperature and circadian sleep-wake rhythms. Intravenous ketamine, an anesthetic that appears to be better tolerated by children than adults, has previously been investigated for treatment of depression in adults with unipolar or bipolar depression.

**Methods**: A systematic chart review identified 12 patients with BD-FOH who had received treatment with ketamine and who had 1 immediate pretreatment symptom assessment and ≥2 posttreatment ratings extending over at least 2 months. The 12 patients (10 boys) ranged in age from 6 to 19 years and had bipolar I disorder with psychotic symptoms and significant impairment. All patients had failed to respond to trials of mood stabilizers, antipsychotics, and benzodiazepines, usually used in combination. Ketamine was administered using an inhaler, in metered 10-mg doses. Dose adjustments were made every 3–6 days until remission of primary symptoms occurred. Doses ranged from 30 mg to 120 mg, every 3–7 days.

**Results**: In all 12 patients, ketamine administration was followed by therapeutic response, usually within 1 hour. The effects typically lasted for 3–4 days, followed by a dramatic return of symptoms. The children had marked reductions in all 10 symptom domains measured by the Child Bipolar Questionnaire. Reductions in all subscales were statistically significant, in most cases meeting extreme levels of significance. Children had a 48% reduction in scores for symptoms associated with FOH (p<0.0001). The patients experienced marked improvement in manic/hypomanic and depressive symptoms; carbohydrate cravings; sleep; fear of harm; and thermoregulatory problems. The 4 types of aggression measured by the Overt Aggression Scale all decreased significantly. Treatment was associated with marked reduction in aggressive obsessions (p<0.005) but not in other types of obsessions measured by the Yale-Brown Obsessive Compulsive Scale.

Dissociative effects related to ketamine were generally mild to moderate and resolved within the first hour after treatment without medical intervention; however, some patients did report severe effects. Most children developed tolerance to the side effects with repeated treatment, and no patient discontinued treatment as a result of these effects.
Discussion: These results must be interpreted cautiously and they require replication in double-blind placebo-controlled trials. However, the rapid and near complete resolution of symptoms in these particularly difficult-to-treat patients suggests intranasal ketamine may be a safe and effective therapy.

Papolos D, Teicher M, Faedda G, Murphy P, et al: Clinical experience using intranasal ketamine in the treatment of pediatric bipolar disorder/fear of harm phenotype. *Journal of Affective Disorders* 2012; doi 10.1016/j.jad.2012.08.040. From the Juvenile Bipolar Research Foundation, Maplewood, NJ; and other institutions. Funded by the Juvenile Bipolar Research Foundation; and the NIMH. The authors declared no conflicts of interest.

**Low-Dose Naltrexone for Pathologic Skin Picking**

Pathologic skin picking occurs with several psychiatric disorders and can lead to serious complications including infection. The exact etiology of pathologic skin picking is unknown. It has been hypothesized to be part of the obsessive-compulsive spectrum, a learned behavior reinforced by positive social responses, and an addiction behavior. SSRIs and exposure/response prevention, both mainstays of OCD treatment, may be helpful. A recently reported case of effective treatment with the opioid antagonist naltrexone lends support to the addiction behavior hypothesis.

A 15-year-old boy with Prader-Willi syndrome was receiving 5 mg/day risperidone for affective symptoms, cycloid psychosis, and aggression. In addition to these symptoms, the patient regularly engaged in serious skin-picking behaviors that resulted in frequent infections. A trial of 200 mg/day sertraline did not improve the skin picking, and behavior modification plans were initiated. Behavioral therapy was continued for 2 years with frequent modifications, but skin picking did not improve. A trial of naltrexone, initiated at 25 mg/day and increased to 50 mg/day after 7 days, was undertaken. Within 1 week of reaching the target naltrexone dose (the low end of the effective dose for addictive disorders), the skin picking decreased. Within 1 month, the pathologic skin picking stopped. Following 3 days of missed treatment because of a supply interruption, the patient’s skin picking reemerged, but it again disappeared 3–4 days after naltrexone was restarted.

The patient reported no adverse effects of naltrexone treatment over 15 months. However, it should be noted that the medication is contraindicated in patients with liver failure and may cause serious hepatocellular injury in overdose.

Banga A, Connor D: Effectiveness of naltrexone for treating pathologic skin picking behavior in an adolescent with Prader-Willi syndrome. *Journal of Child and Adolescent Psychopharmacology* 2012;22 (October):396–398. From the University of Connecticut School of Medicine, Farmington. One study author disclosed financial relationships with commercial sources.

*Drug Trade Names:* naltrexone—ReVia; risperidone—Risperdal; sertraline—Zoloft

**Lifestyle Factors and ADHD Symptoms**

In a large sample of German children and adolescents, ADHD symptoms were associated with poor food choices and increased TV watching. This finding adds to previous evidence that ADHD is associated with obesity and suggests that clinicians should recommend that parents of children with ADHD monitor their diet and TV watching.

Methods: Investigators analyzed data from the cross-sectional German Health Interview and Examination Survey for Children and Adolescents. The sample consisted of 9428 participants, aged 6–17 years. ADHD symptoms were assessed with the parent-rated Strengths and Difficulties Questionnaire (SDQ), which includes the hyperactivity/inattention (HI) subscale of 5 items describing inattentive or hyperactive behavior. Youths (depending on age) or parents were asked about daily TV viewing and leisure exercise of moderate to high intensity.
Diet was assessed with the Food Frequency Questionnaire, and nutritional quality with the Healthy Nutrition Score for Kids and Youth.

**Results:** Nearly 8% of study participants had SDQ-HI scores indicating abnormal levels of hyperactivity/inattention, and approximately 6% were considered borderline. Parental variables such as body mass index (BMI), smoking, diet, health behaviors, socioeconomic status, and status as an immigrant were strongly associated with hyperactivity/inattention in the children; therefore the analysis was adjusted for all available parental factors.

Hyperactivity/inattention was associated with negative health behaviors in the children and adolescents. After adjusting for parental factors, child age and gender, and other SDQ subscales, elevated SDQ-HI scores were associated with TV and video exposure, poor nutritional quality, caloric density of food and beverages, intake of energy from beverages, and level of physical activity ($p \leq 0.04$). ADHD symptoms were not associated with food volume, which may suggest poor food choices are the culprit rather than consumption of a high volume of food.

A gender-specific analysis found the association of SDQ-HI with poor dietary quality was stronger in girls than in boys. Associations with food volume and energy intake from food were significant only in girls.

**Discussion:** This study had several important limitations, including the use of cross-sectional and self-reported data as well as not controlling for ADHD medication use. However, these results suggest that the known association of poor health behaviors with ADHD is not entirely explained by parental variables or other psychopathology of the children. They also suggest that children with ADHD may benefit from efforts to improve food choices and to reduce TV viewing. Efforts to promote healthy behaviors in children with ADHD should also address parental behavior.

van Egm ond-Frohlich A, Weghuber D, de Zwaan M: Association of symptoms of attention-deficit/hyperactivity disorder with physical activity, media time, and food intake in children and adolescents. PLOS One 2012;7:e49781. From SMZ-Ost Donauspital, Vienna, Austria; and other institutions. *Funded by the German Federal Ministry of Health; and other sources. The authors declared no conflicts of interest.*

### Polyunsaturated Fatty Acids for ADHD

Adding polyunsaturated fatty acids (PUFAs) to stimulant medication had no effect on symptoms or on stimulant doses in a randomized, placebo-controlled trial in children with ADHD.

**Background:** Previous open-label trials have shown improvement of ADHD symptoms in children who receive PUFAs. Results of controlled trials have been inconclusive, and a meta-analysis showed a small but statistically significant positive effect of omega-3 fatty acids.

**Methods:** The present study was conducted to investigate adjuvant use of PUFAs in 40 children receiving flexibly-dosed methylphenidate for treatment of ADHD. Study participants, aged 6–12 years, were randomly selected from among patients at an outpatient child psychiatry clinic. All patients received methylphenidate, titrated to 1 mg/kg/day initially, with weekly dose adjustments at the clinician’s discretion; plus they were randomly assigned to receive adjunctive PUFAs or placebo for 10 weeks. The daily PUFA supplement provided 241 mg docosahexaenoic acid (DHA), 33 mg eicosapentaenoic acid (EPA), and 180 mg omega-6. Treatment outcome was measured with the Parent ADHD Rating Scale, administered every 2 weeks, and response was defined as a ≥25% decrease in symptom score.

**Results:** Both treatment groups experienced about a 65% decrease in Parent-Rated ADHD Rating Scale symptoms over the course of the study. Total scores did not differ significantly between the groups at any time point. Ratings on the Inattention and Hyperactivity
subscales did not differ; nor did the methylphenidate dose. The decrease in impulsivity scores was significantly greater in the PUFA-treated children after adjustment for age, gender, and methylphenidate dose. A total of 19 patients in each group achieved response by week 10; this included 13 subjects in the PUFA group (65%) and 17 subjects in the placebo group (85%) who achieved a ≥50% reduction in Parent ADHD Rating Scale score. Common adverse effects (i.e., headache, loss of appetite, agitation) developed in similar proportions of the treatment groups.

Discussion: The sample size of the present study is within the range of the larger-scale studies that reported a positive effect of PUFAs. The inconsistency of study results may be attributed to administration of different types and doses of fatty acids, use of different outcome ratings, or other design issues. The authors do not recommend use of adjunctive PUFAs given the present state of evidence.

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

Assareh M, Ashtiani R, Khademi M, Jazayeri S, et al: Efficacy of polyunsaturated fatty acids (PUFA) in the treatment of attention deficit hyperactivity disorder: a randomized, double-blind, placebo-controlled clinical trial. Journal of Attention Disorders 2012; doi 10.1177/1087054712463962. From Alborz University of Medical Sciences, Karaj, Iran; and other institutions. Funded by Shahid Beheshti University of Medical Sciences, Tehran, Iran; and other sources. The authors declared no conflicts of interest.

Drug Trade Names: methylphenidate—Ritalin, and others

*See Reference Guide.

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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