Oxytocin Improved Social Behaviors in Autism

In a 16-year-old girl with autism, long-term administration of oxytocin via nasal spray dramatically reduced irritability and aggressive behavior and improved social interactions and communication.

The patient, who was high-functioning, presented for evaluation of incomprehension of others’ mind, aggressive behavior including self-injury, and marked impairment in social interactions. Her score on the Aberrant Behavior Checklist (ABC), completed by her mother, was 69 (very high), with individual items indicating hyperirritability, aggression, bizarre behaviors, and poor empathy. She received a diagnosis of autism and underwent several months of treatment with behavioral therapy and psychoeducation, in addition to trials of risperidone and antianxiety agents. Her symptoms did not improve, and she experienced extrapyramidal symptoms and drowsiness associated with the medication.

After reading about oxytocin use for autism on the internet, the patient’s mother began giving her intranasal oxytocin at 8 IU/day, a lower dosage than used in reported cases. The girl’s social behavior began to improve after 1 month of use. She spent less time alone in her room, greeted other people and made small talk, showed empathy, and interacted positively with her family. She sometimes lost her temper but calmed down immediately. After 2 months on oxytocin, her ABC score had decreased to 15, with marked declines in the Irritability and Agitation item and the Hyperactivity and Noncompliance item. After 6 months on oxytocin, the patient’s ABC score was 7. The Clinical Global Impression–Severity scale score decreased from 6 (severely ill) to 3 (mildly ill). There were no obvious adverse effects of oxytocin, no menstrual irregularity or breast milk expression, and no abnormal laboratory or brain MRI findings.

These authors previously reported successful treatment with oxytocin over 1 year in a boy with autism. There have been reports of single-dose treatment in girls, with positive results.
In healthy subjects, a single dose of oxytocin induces feelings of trust, empathy, and longer eye contact. In individuals with autism, single-dose oxytocin has been observed to improve emotional recognition and social behavior. Questions remain about the long-term safety of oxytocin, its wider physiologic effects, and particularly about gender-specific adverse effects.


Drug Trade Names: oxytocin, intranasal—Syntocinon Spray, and others; risperidone—Risperdal

Pharmacotherapy in Autism: Evidence Is Limited

Despite widespread prescription of psychotropic medications for autism spectrum disorders (ASDs), controlled studies of its use have been limited. A recent review of controlled trials suggests that while pharmacotherapy may be useful in controlling comorbid symptoms in some patients, no medication specifically improves the core symptoms of autism.

The authors reviewed English-language, randomized, controlled trials published between 1990 and 2010 that evaluated commonly used drugs in ASDs. They identified 24 studies: 7 each of antipsychotic agents and antidepressants; 4 of stimulants; 1 of atomoxetine; 2 of clonidine; and 3 of anticonvulsants.

Atypical antipsychotics such as risperidone and aripiprazole have become the predominant agents for treating aggressive and disruptive behaviors in ASDs. Studies have been conducted using the Aberrant Behavior Checklist–Irritability (ABC-I) and Hyperactivity (ABC-H) subscales and the Clinical Global Impression (CGI) scale as outcome measures. Risperidone resulted in decreases in CGI scores in 1 study in adults and in improvements of ABC-I scores in 3 studies of children and adolescents. Aripiprazole was also shown to be effective in 2 randomized trials, but both studies reported weight gain as a significant side effect. Haloperidol may be a useful alternative to atypical antipsychotics in patients who cannot tolerate them or do not experience response. In 1 study, haloperidol was superior to placebo in reducing ABC-I and ABC-H scores.

Antidepressants are used to treat irritability and aggression, in addition to depression, in patients with an ASD. Tricyclics are seldom prescribed today, but clomipramine was evaluated in 2 clinical trials since 1990, with mixed results. SSRIs are the most commonly used antidepressant class. In adults, fluvoxamine resulted in improvement in repetitive thoughts and behaviors, aggression, and overall behavioral symptoms. In children, the effects of fluvoxamine depended on serotonin transporter gene polymorphism. Fluoxetine was associated with improvement in obsessions in 1 study in adults and repetitive behaviors in another in children. Citalopram was found to be ineffective in reducing repetitive behaviors in children with autism.

Stimulants, atomoxetine, and clonidine are used to treat ADHD-like symptoms in patients with an ASD. Recent studies, including the large RUPP Autism Network study, have shown positive effects on hyperactivity. Two small studies evaluated methylphenidate primarily for aggression in a total of 23 prepubertal children. Both studies, conducted as placebo-controlled crossover trials, showed significant improvement in ABC-I scores.

Anticonvulsants are often used to treat seizures, which occur in about 30% of patients with autism, and also to treat aggression, mood swings, and hyperactivity, even in the absence of seizures. Of 3 studies of valproate, 1 showed improvement in repetitive behaviors and the other 2 had conflicting results with regard to irritability and other behavioral symptoms.
The evidence suggests drugs can be helpful in treating comorbid symptoms in some patients with autism, but effects are modest at best. When used judiciously in combination with educational and behavioral interventions, they can contribute to lifelong management of these disorders.

Mohiuddin S, Ghaziuddin M: Psychopharmacology of autism spectrum disorders: a selective review. Autism 2012; doi 10.1177/1362361312453776. From the University of Michigan, Ann Arbor. This review was conducted without funding. The authors did not disclose potential conflicts of interest.

Drug Trade Names: aripiprazole—Abilify; atomoxetine—Strattera; citalopram—Celexa; clomipramine—Anafranil; clonidine—Catapres; fluoxetine—Prozac; fluvoxamine—Luvox; haloperidol—Haldol; methylphenidate—Ritalin, and others; risperidone—Risperdal; valproate—Depakene, Depakote

**Theory of Mind fMRI Predicts Anorexia Outcome**

Results of functional MRI studies in patients with anorexia nervosa identified hypoactivation in brain networks that support theory of mind (ToM; the ability to understand mental states of other people), which in turn predicted poorer outcomes 1 year after acute treatment. This finding suggests treatment of anorexia nervosa might be tailored to deficits identified in social cognition.

**Methods:** Study participants were 19 adolescent women, aged 12–18 years, with anorexia nervosa and 21 healthy female controls, matched for age, IQ, and educational level. Patients were hospitalized for multimodal treatment consisting of weight management and re-feeding, training of eating behavior, psychotherapy, and family therapy. Patients underwent fMRI studies a mean of 17 days after admission and again at discharge, an average of 107 days after admission. Controls also underwent the tests twice, separated by about 213 days on average. Overall outcome of anorexia treatment was assessed using the Morgan-Russell Average Outcome Score.

The fMRI test was conducted using a standard method to identify theory of mind activity. Patients viewed videos of moving geometric shapes representing 3 conditions. For the condition that could be interpreted as social (the ToM task), participants were asked to decide whether the shapes were "friends." For 2 other, non-ToM types of videos, they were asked to decide whether the shapes were equally "strong."

**Results:** At both time points, the 2 groups differed significantly in brain activation during the ToM task, with reduced activation in patients with anorexia relative to their performance on the non-TOM task and greater activation in control subjects than in patients. Reduced activation in patients with anorexia was observed in the middle and anterior temporal cortex and in the medial prefrontal cortex. In addition, reduced brain activation within the right medial prefrontal cortex before hospitalization was associated with worse clinical outcome at 1-year follow-up.

**Discussion:** Previous studies have identified deficits in ToM in patients with anorexia nervosa, particularly in acute disease. It is not known whether these deficits are reversible. Emerging evidence for deficits in specific social-cognitive abilities, such as ToM or emotion recognition, support the use of social skills training as an adjunct to standard therapies for anorexia. Social skills training might also be an intervention for presymptomatic anorexia in persons identified with a social-cognitive endophenotype that places them at risk.

Schulte-Ruther M, Mainz V, Fink G, Herpertz-Dahlmann B, et al: Theory of mind and the brain in anorexia nervosa: relation to treatment outcome. Journal of the American Academy of Child and Adolescent Psychiatry 2012;51 (August):832–841. From the University Hospital Aachen, Germany; and other institutions. Funded by the Bundesministerium fur Bildung und Forschung. Three authors disclosed relationships with commercial sources; the remaining 2 reported no conflicts of interest.
New Screening Instrument for Preschool-Aged Children

The Preschool Pediatric Symptom Checklist (PPSC) is a new, freely available screening tool for social/emotional problems that is suitable for completion by parents in the pediatric waiting room.

Several evaluation questionnaires are currently available for preschool children, but their use in screening is limited by length, cost, or complexity. The Pediatric Symptom Checklist (PSC), a feasible and highly popular screening tool, was designed for use in patients aged 6–12 years, although some studies support its use in children as young as 4. The PPSC, like the PSC, was designed to maximize feasibility in clinical settings. It is freely available, easy to score, brief enough to administer in the waiting room, and comprehensible to parents from a variety of cultural and educational backgrounds. It can be used to track children’s behavior longitudinally across the age range and can be readily converted to electronic formats.

The initial PPSC questionnaire items were developed by investigators and reviewed by panels of clinical experts and parents of young children. The scale was constructed, validated, and replicated in 3 samples of parents of children attending pediatric primary care and referral clinics. The final scale consists of 18 items, with an average reading level of grade 1.8. Each question about a potential problem has 3 possible responses: "not at all," "somewhat," and "very much." The items fall into 4 domains of interest: clusters for externalizing, externalizing, and attention problems, and parenting challenges.

Testing in various samples showed that using the Child Behavior Checklist as a reference, the PPSC had sensitivity and specificity* of >0.80 in identifying children with symptoms within a clinical range. Sensitivity and specificity in comparison to parent-reported clinical diagnoses was also high for most disorders. The accuracy of the scale did not differ according to parent education, child race, ethnicity, gender, or age. The authors recommend using a cutoff of 9 for the total score and caution against interpreting item clusters when using the scale.

Sheldrick R, Henson B, Merchant S, Neger E, et al: The Preschool Pediatric Symptom Checklist (PPSC): development and initial validation of a new social/emotional screening instrument. Academic Pediatrics Published online August 24, 2012; doi 10.1016/j.acap.2012.06.008. From the Floating Hospital for Children Tufts Medical Center; and Massachusetts General Hospital, Boston. Funded by The Commonwealth Fund and the NIH. The authors reported no conflicts of interest.

*See Reference Guide.

Family Risk Questionnaire Assists Bipolar Diagnosis

A short checklist to gather information about family history of mood disorders may improve the diagnosis of pediatric bipolar disorder, according to a feasibility study.

Methods: The study authors developed a brief questionnaire about family history of mood disorders and related problems—the Family Index for Risk of Mood Issues (FIRM)—which is freely available as part of the study publication. The checklist includes 5 problem areas: suicide; alcohol or drug problems; admission to a mental hospital; depression; and mania or bipolar disorder. Five categories of relatives of the adult informant were included, ranging from grandparents and aunts and uncles to other children. The questionnaire was administered to adult caregivers seeking outpatient evaluation for 273 young patients, aged 5–18 years. Formal diagnoses of the children were made by expert consensus, based on data form the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (KSADS-PL), with supplemental mood questions.

Results: Bipolar spectrum disorder was diagnosed in 43 youths, 16% of the total. Disorders that are difficult to distinguish from bipolar disorder were highly prevalent in the sample:
ADHD (64%), oppositional defiant disorder (41%), unipolar depression (31%), and conduct disorder (11%). The median number of Axis I diagnoses was 4 in the entire sample and 4.8 in the patients with bipolar disorder.

Family members were able to complete the questionnaire quickly and without difficulty, despite varied educational levels. The questionnaires were more than 99% complete. Of the adults, 22% did not indicate any relatives with mood problems. Among those who did, the median number of problems was 3.7.

The number of risk factors (FIRM Total Score) was significantly higher for children with bipolar disorder than for others in the sample. The score was not predictive of ADHD, oppositional defiant disorder, or conduct disorder. It was associated with depression, which suggests the results may be specific to mood disorders. The FIRM Total Score contributed significant additional information when combined with other questionnaires—the Child Behavior Checklist Externalizing Problems Score, the Mania Scale of the Parent General Behavior Inventory, and the Mood Disorder Questionnaire, Parent Version. After controlling for the results of these checklists, the FIRM predicted a 10–15% increase in the risk of bipolarity for each additional family problem identified.

The FIRM was not sufficiently sensitive or specific to be used as a first-line diagnostic instrument. The investigators tested the optimal clinical application of the FIRM using various statistical approaches. They recommend using the FIRM as a supplemental screening tool with the other clinical assessments and scales normally administered at intake and to stratify youths’ risk for bipolar disorder as high, moderate, or low using a nomogram approach.

Algorta G, Youngstrom E, Phelps J, Jenkins M, et al: An inexpensive family index of risk for mood issues improves identification of pediatric bipolar disorder. Psychological Assessment 2012; doi 10.1037/a0029225. From the University of North Carolina, Chapel Hill; and other institutions. Funded by the NIMH; and other sources. Several study authors disclosed financial relationships with commercial sources.

*See Reference Guide.

Neurofeedback Improves ADHD Core Symptoms

In a randomized trial, neurofeedback was as effective as methylphenidate at reducing core symptoms of ADHD in children and adolescents. This observation supports the use of neurofeedback in patients who do not respond to medications or whose parents prefer a nonpharmacologic approach.

Methods: Neurofeedback is designed to change certain types of EEG activity. In the present study, participants played video games or watched a film while receiving feedback and attempting to regulate their brainwave activity to enhance beta (16–20 Hz) and suppress theta (4–7 Hz) waves. Study participation was offered to all patients referred to a hospital-based clinic over a 3-year period. Eligible subjects were aged 6–18 years, had a diagnosis of ADHD, and had an IQ in the normal range. Patients were randomly assigned to receive 1 of 3 treatments: neurofeedback, methylphenidate (Ritalin), or both treatments. Neurofeedback was conducted 3 times a week for a total of 30 sessions, which included 30 minutes of feedback plus a 5-minute pre- and post-evaluation period. Methylphenidate was administered at 1 mg/kg b.i.d. The primary outcomes, attention and hyperactivity, were measured using the Clinician’s Manual for the Assessment of Disruptive Behavior Disorders–Rating Scale for Parents.

Results: Of 275 children and adolescents who were referred and met the study's criteria, 120 agreed to participate and 91 completed the treatment protocol. There were 13 dropouts from the neurofeedback group, 15 from the medication-only group, and 11 from the combined-treatment group. Nearly all of these patients withdrew before starting randomized treatment as a result of either their parents’ or their own wishes.
Parents of children in all groups reported significant improvement on the rating scales. There were no significant between-group differences on any outcome measure. Improvement in hyperactivity was large, with effect sizes* ranging from 1.75 to 2.88 (p<0.001). Effect sizes for attention were much more modest but still statistically significant (p<0.001). Effect sizes were largest for the neurofeedback-only group, but the study’s statistical power was too low to conclude superiority.

Discussion: Although results of this study and others support the use of neurofeedback in ADHD, nonspecific factors may contribute to its effects. These include the large amount of time spent with the therapist, better motivation among patients who choose this option, and incidental cognitive-behavioral training introduced during treatment. The results are noted to be contrary to those of prior studies in which combined treatment was most effective.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial, but no blinding was involved as symptom ratings were completed by parents.

Duric N, Assmus J, Gundersen D, Eigen I: Neurofeedback for the treatment of children and adolescents with ADHD: a randomized and controlled clinical trial using parental reports. BMC Psychiatry 2012;12:107. From Helse Fonna Haugesund Hospital, Haugesund, Norway; and other institutions. Funded by the Solveig and Johan P. Sommers Foundation; and National Competency Center for AD/HD in Norway. The authors declared no conflicts of interest.

*See Reference Guide.

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Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance and large effect sizes do not ensure treatment efficacy.

Sensitivity and Specificity: Statistical measures of the performance of binary classification tests. Sensitivity measures the proportion of actual positives that are correctly identified (i.e., the percentage of sick people who are correctly identified as having the condition). Specificity measures the proportion of negatives that are correctly identified (i.e., the percentage of healthy people who are correctly identified as not having the condition). A perfect predictor would have 100% sensitivity and specificity.

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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