Fam ily Intervention for Adolescent Suicidality

In a preliminary, controlled trial, a brief family intervention reduced adolescent suicidality and other psychiatric symptoms.

Methods: The study examined the effects of a strengths-based family education program, called the Resourceful Adolescent Parent Program (RAP-P), on suicidality in 48 adolescents who had engaged in ≥1 episode of suicidal behavior (i.e., deliberate self-injurious behavior or suicidal ideation, intent, or attempt) in the 2 months before referral. Participants were recruited from emergency departments and community mental health clinics in a disadvantaged part of Sydney, Australia. All study participants received usual care, which could include any combination of psychoeducation; crisis management; nonspecific and/or supportive counseling; cognitive behavioral therapy; and pharmacotherapy. Half of the participating families were randomly assigned to receive RAP-P in addition to usual care. As provided in the study, RAP-P consisted of a manualized interactive psychoeducation program for parents, delivered in 4 sessions (2 hours each), either weekly or biweekly. The sessions were individual and could be delivered at the clinic or in the family’s home. Adolescents did not participate in the RAP-P program. The primary study outcome, suicidality, was measured using the short self-report Adolescent Suicide Questionnaire-Revised (ASQ-R), which was completed by adolescents after their parents finished the program (or after a similar interval in controls) and again at 6 months.

Results: Study subjects had a mean age of 15 years, and about 75% were female. All had major depressive disorder, and many had additional disorders such as obsessive-compulsive disorder, anxiety, or complex posttraumatic stress disorder associated with a history of trauma (e.g., sexual abuse or exposure to domestic violence). The mother was the participating parent in nearly all cases. Two families dropped out of the RAP-P group, and 6 dropped out of the usual-care-only group. Parents assigned to RAP-P attended >90% of the scheduled sessions and after completing the program, most rated it as “very interesting” and “very helpful”.
Both groups demonstrated a significant decrease in suicidality over the follow-up time (p<0.001), but the adolescents whose parents received RAP-P showed larger improvements than controls. The mean baseline ASQ-R score was 12 in each group. At 6-month follow-up, scores were reduced to 7 and 11 in the RAP-P and usual-care groups, respectively (p<0.05).

Differences in the Strengths and Difficulties Questionnaire, which measures emotional and behavioral adjustment, also favored the RAP-P group, as did results of a blinded clinician questionnaire on mental health, behavioral functioning, and social impairment. The improvement in suicidality with RAP-P was partially mediated by improved family functioning and partially by nonspecific effects of the program.

Discussion: Suicide is among the leading causes of death for young people, and negative family climate appears to be an important risk factor for suicidal behavior. Although they require replication, the results of this study suggest a brief, structured, and well-received parent intervention can improve family function and thus reduce adolescent suicidality.

Pineda J, Dadds M: Family intervention for adolescents with suicidal behavior: a randomized controlled trial and mediation analysis. Journal of the American Academy of Child and Adolescent Psychiatry 2013;52 (August):851–862. From the University of New South Wales, Sydney, Australia. Funded by the Rotary Health Research Fund Australia; and other sources. The authors declared no conflicts of interest.

Lisdexamfetamine and Quality of Life

Treatment with lisdexamfetamine was associated with improved health-related quality of life (HRQoL) and functional outcomes in children and adolescents with ADHD participating in a 7-week, manufacturer-sponsored clinical trial. This report describes secondary outcomes from a pivotal clinical trial of lisdexamfetamine that also showed efficacy for the primary outcome, ADHD symptoms.

Methods: Study participants were 317 children and adolescents with ADHD of at least moderate severity. Patients were given lisdexamfetamine at 30, 50, or 70 mg/day; OROS methylphenidate at 18, 36, or 54 mg/day; or placebo. OROS methylphenidate was used as an active control to establish the validity of the trial and was not compared directly with lisdexamfetamine. Patients underwent dose optimization for 4 weeks, and then received a stable dose for 3 weeks. HRQoL was measured with the parent-reported Child Health and Illness Profile-Child Edition (CHIP-CE), which consists of 5 domains and 12 subdomains. Functional impairment was rated with the 6-domain Weiss Functional Impairment Rating Scale–Parent Report.

Results: At baseline, patients had markedly reduced ratings for the achievement domain of CHIP-CE, which was pre-specified as the primary HRQoL outcome in this study. Within this domain, baseline scores were low in the subdomains of academic performance and peer relations. Baseline scores for the risk avoidance, resilience, and satisfaction domains were also well below population normative means. After treatment, achievement scores increased significantly in patients who received lisdexamfetamine (effect size,* 1.28; p<0.001). Significant improvements were also observed in the risk avoidance, resilience, and satisfaction domains and in most subdomains. (See table.) Of the 5 domains, only comfort was unimpaired at baseline in the children with ADHD and unaffected by treatment. HRQoL results were similar in the OROS methylphenidate group.

<table>
<thead>
<tr>
<th></th>
<th>Achievement</th>
<th>Risk Avoidance</th>
<th>Resilience</th>
<th>Satisfaction</th>
</tr>
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<tbody>
<tr>
<td>Lisdexamfetamine</td>
<td>1.28; p&lt;0.001</td>
<td>1.08; p&lt;0.001</td>
<td>0.42; p&lt;0.01</td>
<td>0.37; p&lt;0.05</td>
</tr>
<tr>
<td>OROS Methylphenidate</td>
<td>0.91; p&lt;0.001</td>
<td>0.95; p&lt;0.001</td>
<td>0.40; p&lt;0.05</td>
<td>0.35; p&lt;0.05</td>
</tr>
</tbody>
</table>
Among the 6 functional impairment domains, the greatest deficits at baseline were observed for the family domain and the learning and school domain. Lisdexamfetamine was associated with significant improvement in total scores on the functional questionnaire (effect size, 0.924; p<0.001). Statistically significant gains were also seen in the learning and school, family, social activities, and risky activities domains. Results with OROS methylphenidate were similar to lisdexamfetamine.

Discussion: Optimal management of ADHD includes not only symptom reductions, but improved quality of life and reduced functional impairment. Results of this analysis indicate that both lisdexamfetamine and OROS methylphenidate produce substantial improvements in these domains, with the greatest effects in the domains that showed the most impairment at baseline.

Banaschewski T, Soutullo C, Lecendreux M, Johnson M, et al: Health-related quality of life and functional outcomes from a randomized, controlled study of lisdexamfetamine dimesylate in children and adolescents with attention deficit hyperactivity disorder. CNS Drugs 2013; doi 10.1007/s40263-013-0095-5. From the University of Heidelberg, Mannheim, Germany; and other institutions. Funded by Shire Pharmaceuticals. All study authors disclosed financial relationships with commercial sources, including Shire, the manufacturer of Vyvanse.

Drug Trade Names: lisdexamfetamine—Vyvanse; OROS methylphenidate—Concerta

*See Reference Guide.

Suicide Toxicology: No Link to Antidepressants

Youth suicides increased in Sweden during the years after the FDA and the European authorities issued "black box" warnings about the risk of antidepressants and suicide in young people. Toxicological data indicate that the increase occurred largely in adolescents who were not receiving treatment with antidepressants. This finding adds to the growing evidence that the "black box" warnings were counterproductive.

Methods: Data were analyzed for all persons, aged 10–19 years, who committed suicide during 2 periods: 1992–2002 and 2003–2010. In Sweden, all deaths that appear unnatural are investigated by forensic pathologists who screen for about 200 substances, including all available antidepressants. The analysis also included aggregate data on antidepressant prescriptions during 1999–2010 and individual-level prescription data after 2005.

Results: The use of antidepressants in Swedish youths increased between 1999 and 2002. During this period, there were 407 suicides, ranging from 29 to 47 each year. Antidepressants were detected in the toxicology screens of ≤4 suicides per year. Among the 52 confirmed or possible suicides in 10- to 14-year-olds, only 1 unconfirmed case was associated with an antidepressant.

The annual rate of antidepressant use remained steady for several years after 2003 (warnings were added in 2004), and began to increase again in 2007. Suicides increased for 5 consecutive years after 2003, reaching a peak of 69 in 2008 and decreasing somewhat in 2009 and 2010. There were 438 youth suicides in the 8 years after 2003, compared with 407 in the previous 11 years.

Despite the increase in total annual suicides, the number of patients who received an antidepressant and committed suicide in 2008, the peak year, was only 2 more than in 2003—8 vs. 6. Among 35 children who were aged 10–14 years and who committed suicide after 2003, only 1 had a positive screen for an antidepressant; another had received a prescription for an antidepressant but had apparently not taken it.

Individual-level data showed that only 20% of young people who committed suicide between 2006 and 2010 had been given a prescription for an antidepressant in the prior 6 months. Of this group, two-thirds filled >1 prescription, suggesting compliance, and about that many had the drug detected on postmortem toxicology—i.e., about 12% of all suicides during this period.
Discussion: These results provide further support for the suggestion that the increase in adolescent suicides observed in some countries after the "black box" warnings may have been a result of the warning. In Sweden, the effect of the "black box" seems to have come to an end in 2007, after which antidepressant use increased and the annual number of suicides decreased. There was, however, a trend for antidepressants to be discovered more often in the toxicology of suicides over the 2 decades of the study. This reflects the growing use of antidepressants in the population and is likely related to the failure of antidepressants to prevent suicide in some patients.

Isacsson G, Ahlner J: Antidepressants and the risk of suicide in young persons—prescription trends and toxicological analyses. *Acta Psychiatrica Scandinavica* 2013; doi 10.1111/acps.12160. From the Karolinska Institutet, Stockholm; and the National Board of Forensic Medicine, Linkoping, Sweden. *Funded by the Karolinska Institutet and Stockholm County Council. The authors declared no conflicts of interest.*

Stimulant-Associated Cough

An 8-year-old girl with ADHD was referred by her pediatrician to an allergist with a 7-month history of chronic cough. The patient’s cough was dry and nonproductive and occurred on a daily basis. Treatments for possible atypical pneumonia, allergic rhinitis, and asthma (e.g., antibiotics, oral corticosteroids, antihistamines) had produced no change in the cough. Skin testing revealed no allergen sensitivity, and chest radiographs uncovered no anatomical defects or disease. Physical findings were unremarkable except for the presence of facial motor tics (i.e., repetitive eye blinking, face rubbing). A detailed review of her medication history revealed that the cough had started shortly after she began treatment with 20 mg/day extended-release amphetamine–dextroamphetamine (Adderall XR). The stimulant was stopped, and at the 4-week follow-up, the patient’s caregiver reported that the cough had completely resolved within 48 hours of stopping the drug. The facial tics had also resolved. The patient was started on a different formulation of dextroamphetamine, and the chronic cough did not recur.

Although the mechanism is unclear, a link between psychostimulant use and new-onset tics has been reported and is included in the labeling for the drugs. Phonic tics can include throat clearing and cough and should be considered as a possible cause for chronic cough in patients taking stimulants.

Leibel S, Bloomberg G: Attention-deficit/hyperactivity disorder stimulant medication reaction masquerading as chronic cough. *Annals of Allergy, Asthma and Immunology* 2013;111 (August):82–83. From Washington University School of Medicine, St. Louis, MO. *The authors declared no conflicts of interest.*

N-acetylcysteine in Autism

In a randomized trial, adjunctive N-acetylcysteine (NAC) had small but statistically significant positive effects on behavior in children with autism but did not ameliorate core symptoms of the disorder. This finding provides some support for oxidative stress as a target for treating autism.

Methods: NAC is an antioxidant, available as an over-the-counter supplement, that has been used to treat mental illnesses including schizophrenia and bipolar disorder. In the present study, NAC or placebo were started at the same time as risperidone (Risperdal) in 40 children, aged 3.5–16 years (mean, 8 years), with a diagnosis of autism. Over 2 weeks, NAC was titrated to 1200 mg/day in 2 divided doses. Risperidone was dosed flexibly, with maximums of 2 and 3 mg/day, based on weight. The primary outcome of the 8-week trial was change in score on the irritability subscale of the Aberrant Behavior Checklist (ABC).

Results: Mean risperidone dosages did not differ between the groups (0.76 in the NAC group and 0.92 in the placebo group). Irritability decreased significantly over time in both
treatment groups (p<0.001). After 8 weeks of treatment, the average ABC Irritability score decreased from 13.2 to 9.7 in the risperidone-plus-NAC group and from 16.7 to 15.1 in the risperidone-plus-placebo group (p<0.04; effect size,* 0.14). There was no difference between groups in the other ABC subscales of lethargy and social withdrawal, stereotypic behavior, hyperactivity and noncompliance, and inappropriate speech.

Adverse effects of NAC included constipation, fatigue, nervousness, and daytime drowsiness, each affecting about 13–16% of the children. One patient withdrew from the study because of NAC-associated sedation.

**Discussion:** NAC is a precursor of glutathione, a potent antioxidant that is deficient in children with autism. It has been suggested that an imbalance of oxidative stress and antioxidant defenses contributes to some behavioral symptoms in children with autism. It appears that administration of NAC may increase glutathione and enhance defense against oxidative stress. The results of this study, although limited by small sample size and a short observation period, suggest that NAC supplements may be used to decrease irritability in children with autism.

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

Ghanizadeh A, Moghimi-Sarani E. A randomized double blind placebo controlled clinical trial of N-acetylcysteine added to risperidone for treating autistic disorders. *BMC Psychiatry* 2013 doi: 10.1186/1471-244X-13-196. From Shiraz University of Medical Sciences, Iran. *Funded by Shiraz University of Medical Sciences. The authors declared no conflicts of interest.*

*See Reference Guide.

### Oxytocin Clinical Trial in Autism

In a placebo-controlled trial, repeated treatments with intranasal oxytocin did not improve outcomes in boys with autism spectrum disorders. The finding, which contrasts previously reported positive results, suggests that exogenous oxytocin may only have benefit in certain patients or contexts.

**Methods:** Participants were 38 boys, aged 7–16 years, with an IQ of ≥80 and a DSM-IV diagnosis of autism, Asperger syndrome, or pervasive developmental disorder not otherwise specified. Girls were excluded because evidence suggests they respond differently to oxytocin than boys. Families lived at the study site for the 5-day trial. On 4 consecutive days, patients and their parents completed a family interaction task and parent-child interaction training, in random order. Within half an hour of the parent-child interaction training sessions, patients were administered double-blind, intranasal oxytocin (12 or 24 IU, depending on weight) or placebo. Parent and child behaviors were assessed by clinicians, parents, and independent observers at baseline, daily during treatment, and at a 3-month return visit.

**Results:** Oxytocin did not differ from placebo in its effects on any of the study outcomes—i.e., the social interaction skills of child and parent eye contact, non-verbal behaviors, and verbal content; global social interaction; repetitive behaviors; emotion recognition; and diagnostic change. Most of these factors showed positive changes with time, but equally in the oxytocin and placebo groups. The investigators conducted various analyses to account for this lack of oxytocin efficacy but could not attribute it to small sample size; effects of the different oxytocin doses; effects limited to different age groups; use of concomitant medication; or problems with the drug formulation.

**Discussion:** In previous studies, exogenous oxytocin has had robust effects in enhancing social recognition, which is thought to be a major developmental deficit in autism. Of the few studies of single-dose intranasal or intravenous oxytocin in children or adults, all have shown positive results, including improvements in repetitive behaviors, social memory, and emotion processing.
Children with autism have reduced plasma oxytocin levels and increased levels of oxytocin precursor proteins. The present study suggests autism may also be associated with functional problems in the oxytocin receptor system. Benefits of oxytocin may be limited to patients with a specific receptor variant.

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


*See Reference Guide.

**Mental Health Awareness Campaigns Launched**

According to the Centers for Disease Control and Prevention, 1 in 5 Americans experiences a mental health issue, yet only 1 in 3 receives mental health services. In order to increase understanding and awareness about mental health in young people, the National Association of Broadcasters has launched the "OK2TALK" campaign. The community campaign includes television and radio ads that feature teens and young adults discussing their mental health experiences. The ads attempt to prompt conversation about mental health and to let people know that help is both available and effective. The campaign website, ok2talk.org, encourages teens and young adults to share their personal stories of recovery, tragedy, struggle, or hope, and includes resources for those seeking help. Another new site, mentalhealth.gov, which incorporates the tag line "Let’s talk about it," was launched as part of a national initiative to facilitate discussions about youth mental health. These linked sites encourage honest, open communication about mental health issues, supply information to patients and families about mental illnesses, and provide resources, including referral services, for those needing help.


**Reference Guide**

**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.

**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.