Azithromycin for Acute-Onset OCD

In a placebo-controlled pilot study, azithromycin (Zithromax) reduced the severity of obsessive-compulsive symptoms in children with recent-onset, severe OCD possibly triggered by an infection. This preliminary result is consistent with those of other recent, small studies of various antibiotics for neuropsychiatric symptoms in childhood.

**Methods:** Study participants (n=31) were aged 4–14 years and met criteria for new-onset or relapse of pediatric acute-onset neuropsychiatric syndrome (PANS), with or without a recent group A streptococcal infection (PANDAS). For study inclusion, they were required to be experiencing abrupt or dramatic onset OCD symptoms of at least moderate severity (Children’s Yale-Brown Obsessive Compulsive Scale [CY-BOCS] total score of ≥16 and Clinical Global Impression–Severity* [CGI-S] score of ≥4), as well as ≥2 additional neuropsychiatric symptoms such as anxiety, tics, or frequent urination. Because of the difficulty of confirming a recent infection for each OCD episode, study patients were enrolled irrespective of whether they met criteria for PANS. Participants were randomly assigned to 4 weeks of double-blind treatment with either 10 mg/kg/day azithromycin (maximum dosage, 500 mg/day) or placebo. All children received a probiotic to prevent antibiotic-associated diarrhea. The primary outcome measures were the CY-BOCS and the CGI-S.

**Results:** Of the 31 enrolled children, 24 were receiving medication at baseline including allergy medicines (n=9) and SSRIs prescribed for OCD symptoms (n=3). A total of 19 children had a recent group A streptococcal infection identified as a trigger or associated with the current OCD episode, and 13 had a recent upper respiratory infection. OCD symptoms were present for an average of nearly 10 weeks before study enrollment.

Azithromycin was associated with a larger reduction in the average CGI-S score than placebo: mean scores at week 4 were 4.06 for azithromycin and 4.93 for placebo (p=0.003; effect size,* 1.61). Children receiving azithromycin had a 22% decrease in score, compared with a 1% decrease in the placebo group (p=0.008), with 7 and 1, respectively, meeting criteria for...
response (41% vs 7%; p=0.045). Although numeric differences in CY-BOCS improvement favored azithromycin (30.5% decrease vs 17%; effect size, 0.79), between-group differences were not significant. The number of treatment responders, when defined as a ≥30% reduction in the CY-BOCS score, also did not differ significantly between the groups: 8 vs 3 with azithromycin and placebo, respectively (47% vs 21%). The groups did not differ in change from baseline in tic severity, cognitive function, or mood. Patients with a higher level of tic severity at baseline were more likely to have experienced symptomatic response with azithromycin treatment. No other clinical features, including OCD-onset characteristics or the presence of an infectious trigger, distinguished children more likely to have response to the antibiotic.

**Discussion:** These results suggest antibiotic treatment may reduce rapid-onset OCD symptom severity, particularly in children with moderate-to-severe tics. The efficacy of this treatment was partially obscured by the high rate of placebo response, which may be partially attributable to the intermittent course of OCD in children or to the effects of probiotic treatment.

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

Murphy T, Brennan E, Johnco C, Parker-Athill E, et al: A double-blind randomized placebo-controlled pilot study of azithromycin in youth with acute-onset obsessive–compulsive disorder. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (September):640–651. From the University of South Florida, St Petersburg; and other institutions. **Funded by Massachusetts General Hospital. Three of 7 study authors disclosed relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

### Predictors of Internalizing Problems

Early risk factors, some appearing before school entry, were associated with later escalation of internalizing problems in a longitudinal study of school-aged children.

**Methods:** The analysis was conducted as part of a larger cohort study of Australian children, assessed first at age 4–5 years and then every 2 years thereafter. The analysis included 3153 children with complete, mother-reported data on internalizing problems in the 4 study waves (i.e., ages 4–5 years, 6–7 years, 8–9 years, and 10–11 years). Internalizing problems in the 3 later waves were measured with the Emotional Symptoms subscale of the Strengths and Difficulties Questionnaire (SDQ). The investigators also measured child emotional dysregulation, externalizing problems, teacher-reported peer relations, parenting behaviors, socioeconomic status, and maternal mental health. The analysis was designed to develop models predictive of both the initial prevalence of internalizing problems and the growth trajectory of the problems over the 3 older age waves.

**Results:** Internalizing problems were more likely to occur in girls and in children who at age 6–7 years had greater emotional dysregulation and externalizing problems and who had a mother who reported poorer mental health and a more angry parenting style. In addition, poorer maternal mental health and peer problems in 4–5 year olds were associated with more internalizing problems 2 years later. The growth rate of internalizing problems was increased in girls and in children with higher levels of emotional dysregulation and peer problems at age 6–7 years. Growth was also increased in children who, at age 4–5 years, had higher externalizing problems and peer problems and mothers with poorer mental health. Socioeconomic status was not associated with the initial prevalence or with the growth of internalizing problems.

**Discussion:** Childhood internalizing problems are subject to change, making them potential targets for early intervention. Emotional dysregulation at age 4–5 years may not be as relevant as later dysregulation because many children acquire the ability to regulate themselves when they enter school. Early but not later externalizing problems were strongly predictive of the growth in internalizing problems, perhaps because externalizing problems tend to be stable
over childhood, contributing to greater difficulties and a negative self-image. The study results support the recognized importance of peer interactions and maternal mental health. Attention to social and emotional skill development in children transitioning to school and programs to support maternal mental health could be useful in preventing later internalizing problems.

Wang C, Williams K, Shahaeian A, Harrison L: Early predictors of escalating internalizing problems across middle childhood. School Psychology Quarterly 2017; doi 10.1037/spq0000218. From Charles Sturt University, Bathurst, Australia; and other institutions. Funded by the Australian Government’s Collaborative Research Networks programs. The authors did not include disclosure of potential conflicts of interest.

ADHD Medications and Substance Use Problems

In a longitudinal study that compared within-patient experience, treatment with stimulants or atomoxetine (Strattera) was associated with lowered risk of substance use problems.¹

**Background:** ADHD is associated with increased risk of co-occurring substance use disorders. Many disorder-specific characteristics, including the propensity toward impulsive risk-taking behavior, co-occurrence of mental health and behavioral problems, psychosocial risk factors, and self-treatment of symptoms, likely underlie the association. Concerns have also been raised that stimulant use could sensitize patients with ADHD to the rewarding effects of drugs, thus leading to increased risk of substance use disorders. However, it is also possible that by reducing the ADHD symptoms and impairments, stimulant and other medications may decrease risk for substance use disorder.²

**Methods:** The study cohort was drawn from a large U.S. commercial insurance database. Nearly 3-million enrollees with a diagnosis of ADHD or a prescription for a stimulant or atomoxetine were identified. Atomoxetine was the only non-stimulant included because others are often used as adjunctive or secondary treatments. The analysis excluded individuals aged ≤13 years as well as time periods when individuals did not have prescription coverage. Substance-related events were defined as any emergency department claims with a non-tobacco substance use disorder diagnosis. The investigators conducted 3 analyses: substance-related events in ADHD patients versus matched controls without an ADHD diagnosis; substance-related events in patients with ADHD while on medication versus off medication; and long-term within-individual associations after 2 years.

**Results:** Associations between ADHD mediation and substance-related events differed in men (53% of the ADHD cohort) and women and were analyzed separately. Both male participants (median age, 21 years at the start of follow-up) and female participants (median age, 28 years) with ADHD were more likely than those without ADHD to have a substance-related event. (See table.) In within-individual models that excluded potentially confounding individual-level factors, ADHD medication was associated with a 35% lower risk of substance-related events in men and a 31% lower risk in women. These associations were consistent in subsets of individuals with and without a prior substance use disorder diagnosis, regardless of concurrent psychotropic medication or psychotherapy, and in those experiencing a first substance-related event. The 2-year analysis showed minor increases in risk of substance-related events in both genders, but the overall reduction in risk persisted.

<table>
<thead>
<tr>
<th>Concurrent and longitudinal associations between ADHD medication and substance-related events</th>
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<tr>
<td><strong>Adjustment odds ratio</strong></td>
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<tr>
<td><strong>Male patients</strong></td>
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<td>ADHD vs non-ADHD patients</td>
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<td>Within-individual on vs off medication</td>
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<td>Long-term within-individual</td>
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<td><strong>Female patients</strong></td>
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<tr>
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<tr>
<td>Within-individual on vs off medication</td>
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<td>Long-term within-individual</td>
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</table>
**Discussion:** Accumulating evidence suggests that ADHD medication may protect against not only substance use problems, but related outcomes such as injuries, accidents, criminality, depression, and suicide. In the short term, medications may reduce impulsive decision making. Long-term effects may be the result of changes in habitual behaviors and decisions, but appear to weaken somewhat.

1Quinn P, Chang Z, Hur K, Gibbons R, et al: ADHD medication and substance-related problems. *American Journal of Psychiatry* 2017;174 (September):877–885. From Indiana University, Bloomington; and other institutions. **Funded by the NIMH; and other sources. Three of 10 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**


*See Reference Guide.

**Anxiety Disorder Treatments**

Cognitive behavioral therapy (CBT) and SSRIs are effective in treating anxiety symptoms in children and adolescents, according to a systematic review and meta-analysis of all currently recommended treatments.1 SNRIs are also effective, although supported by a smaller evidence base. All of the treatments are safe and well tolerated.

**Methods:** The meta-analysis included controlled trials and observational studies from a wide scope of sources. Anxiety disorders were examined as a class, excluding only obsessive-compulsive disorder and posttraumatic stress disorder, which are typically treated differently from the other disorders in the class. The analysis included studies of patients, aged 3–18 years, who received CBT, medication, or both. Comparison groups could receive another active treatment, placebo, wait-listing, observation alone, or treatment as usual. In the included studies, CBT consisted of some combination of cognitive restructuring, relaxation training, and exposure therapy and was limited to individual face-to-face sessions with the child, with varying degrees of parent involvement. Non-comparative studies were included if they provided information about adverse events. The primary outcomes of interest were anxiety symptoms, treatment response (loss of principal anxiety diagnosis or Clinical Global Impression (CGI)–Severity* [CGI-S] score of 1 or 2), remission (loss of all anxiety diagnoses or CGI–Improvement* score of 1 or 2), and adverse events.

**Results:** The analysis included 115 studies with a total of >7700 patients. Participants had a mean age of 9 years, and 56% were girls. A total of 40% of studies included children with comorbid non-anxiety disorders. The medications studied were SSRIs, SNRIs, tricyclic antidepressants, and benzodiazepines. Outcomes were compared separately for clinician-, parent-, and child-reported outcomes and for the different control treatments.

SSRIs were significantly superior to placebo for all outcomes, with effect sizes* of 0.42 for child-rated measures, 0.61 for parent-rated measures, and 0.65 for clinician-rated measures. Relative risks* for response and remission with SSRIs were 1.96 and 2.04, respectively. SNRIs were also significantly superior to placebo, but only for clinician-rated measures (effect size, 0.45). No evidence supported the use of tricyclics or benzodiazepines.

CBT was compared with pill placebo, active medications, and various other control conditions for the 3 different types of informant. Results of these comparisons were generally positive, favoring CBT with effect sizes ranging from 0.36 to 1.36. Only 2 studies compared the CBT–medication combination with either treatment alone, both supporting the combination. There were only 2 head-to-head drug comparisons, neither finding a clear advantage for either medication. In a network meta-analysis,* CBT performed as well as any individual medication and all medications pooled.
A total of 82 studies reported adverse events. No serious adverse events were reported for any medication. Of 3 studies with data on suicidality or self-harm, only 1 identified suicidal ideation, in 3 patients receiving venlafaxine (Effexor). Studies were too small or too short to assess suicidality with SSRIs or SNRIs.

Editorial. 2 The summarized evidence suggests that multiple treatments can improve anxiety symptoms substantially. However, there are minimal data on the comparative efficacy of different drugs, and the best-researched drugs are off label for childhood anxiety disorders. In addition, acute treatment is not expected to result in full remission for many children, even those receiving gold-standard therapy.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.


2Asarnow J, Rozenman M, Carlson G: Medication and cognitive behavioral therapy for pediatric anxiety disorders: no need for anxiety in treating anxiety [editorial]. JAMA Pediatrics 2017; doi 10.1001/jamapediatrics.2017.3017. From the University of California, Los Angeles; and the State University of New York at Stony Brook. The authors declared no financial relationships with commercial sources.

*See Reference Guide.

Antidepressant Efficacy in Common Pediatric Disorders

According to the results of a systematic review and meta-analysis, SSRIs and SNRIs are superior to placebo in children and adolescents with common psychiatric disorders, but not by a large margin. 1

Methods: This review assessed the efficacy of second-generation antidepressants—SSRIs and SNRIs—in children and adolescents with depressive disorder, anxiety disorders, obsessive-compulsive disorder (OCD), or posttraumatic stress disorder (PTSD). The analysis included placebo-controlled clinical trials of medication, with or without accompanying psychosocial interventions, in patients aged <18 years. The primary outcomes were those reported by each study, using a standardized, dimensional symptom scale specific to the disorder in question or a general severity scale.

Results: The analysis included 36 trials with a total of 6778 participants. There were 17 trials in depressive disorders, 10 in anxiety disorders, 8 in OCD, and 1 in PTSD. The combined analysis found small drug–placebo difference (see table) that favored active treatment. Medication effects were stronger in anxiety disorders and OCD than in depression, largely because the placebo effects in depression were large. In the comparison between drug categories, SSRIs were superior to SNRIs in anxiety disorders, but not in depressive disorders. No studies investigated SNRIs in OCD or PTSD.

Patients taking antidepressants reported more serious adverse events and treatment-emergent adverse events than those taking placebo. Discontinuation for an adverse event was significantly more common with an antidepressant than placebo (relative risk,* 1.79; p<0.001). Rates of adverse events did not differ between SSRIs and SNRIs.

<table>
<thead>
<tr>
<th>Drug–placebo differences for SSRIs and SNRIs combined in common pediatric psychiatric disorders</th>
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<tr>
<td><strong>Effect Size</strong></td>
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<td>All disorders</td>
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<tr>
<td>Depressive disorders</td>
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<tr>
<td>Anxiety disorders</td>
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<tr>
<td>OCD (SSRIs only)</td>
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<td>PTSD (SSRIs only)</td>
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*C & A PSYCHIATRY ALERTS / October 2017 59
These observations indicate pharmacotherapy offers similar efficacy to that reported for psychological interventions in common pediatric psychological problems, and both fall short of the ideal. Given the potential for harm from medication, psychotherapy may be a preferred first option. Patients who present with these problems may also benefit from simple strategies such as attention and support, education, relaxation, mindfulness, and lifestyle changes. The large placebo effect in depression suggests that in young people, access to care, attention, and support can result in improvement of symptoms.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

*See Reference Guide.

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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.

Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

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.

Network Meta-Analysis: A study design that can provide estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common. For example, if in a clinical trial comparing treatment A with treatment B, option A is determined to be superior, and a separate trial in similar patients found option B superior to a third agent, option C, a network meta-analysis of these 2 trials would allow a researcher to conclude that treatment option A is more effective than option C, even though the 2 options have never been directly compared.

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.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

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 are posted at www.alertpubs.com.