

CHILD & ADOLESCENT PSYCHIATRY ALERTS

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Antidepressants in Anxiety

In children and adolescents with anxiety disorders, antidepressant-related improvements occur quickly and SSRIs are associated with earlier and larger improvement than SNRIs, according to the results of a meta-analysis.

Background: SSRIs and SNRIs have both been recommended as first-line treatment for pediatric anxiety disorders. However, duloxetine is the only FDA-approved antidepressant for this indication, and it is unknown whether SSRIs are superior to SNRIs. The present meta-analysis was conducted to evaluate the trajectory of response to antidepressants in pediatric anxiety disorders and to compare the effects of drug class and dose.

Methods: Studies were included if they were prospective, randomized, parallel-group, placebo-controlled trials that evaluated the efficacy of SSRIs or SNRIs in social, generalized, and/or separation anxiety disorder in patients aged ≤ 18 years. For inclusion, studies were required to use a standardized rating scale to measure anxiety symptoms. The primary outcome of the analysis was change from baseline on a standardized measure of anxiety for the active medication in comparison with placebo. Dose comparisons were based on fluoxetine equivalents of the labeled therapeutic range of each drug. Atomoxetine was included in the analysis because of its potent norepinephrine reuptake blockade and serotonin transporter inhibition.

Results: The comprehensive literature search identified 9 studies conducted in 1805 patients, evaluating 7 different drugs: 4 SSRIs (i.e., fluoxetine, fluvoxamine, paroxetine, and sertraline) and 3 SNRIs (i.e., atomoxetine, duloxetine, and venlafaxine). The median study duration was 10 weeks. The Pediatric Anxiety Rating Scale was the outcome measure in all but 2 studies.

Overall, statistically significant differences between drug and placebo appeared at week 2 ($p=0.005$) and reached a clinically significant effect size* of 0.44 by week 6 ($p=0.001$). Both SSRIs and SNRIs were associated with statistically significant improvement, relative to placebo, at treatment week 2 and remained statistically superior to placebo up to week 12. SSRIs were superior to SNRIs beginning at week 2 ($p=0.026$) and continuing to week 12 ($p<0.03$ for all

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2-week intervals). The results were essentially unchanged in a sensitivity analysis that excluded data from the atomoxetine trial. Industry-funded and government-funded studies had generally similar results. Low doses of SSRIs (<1.5 fluoxetine equivalents per day) were no less effective than higher doses overall, but high doses were associated with an earlier response.

Discussion: These results suggest that SSRIs may be more effective than SNRIs against pediatric anxiety. It is possible that SSRIs could be superior because the serotonin system matures earlier than the noradrenergic system and may be a more available treatment target. In addition, SNRIs have class-specific tolerability concerns, including suicidality with venlafaxine. The study findings regarding dosage raise questions regarding the long-held belief that antidepressants should be titrated.

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

Strawn J, Mills J, Sauley B, Welge J: The impact of antidepressant dose and class on treatment response in pediatric anxiety disorders: a meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry* 2018;57 (April): 235–244. From the University of Cincinnati College of Medicine; and other institutions, OH. **Funded by the NIMH. Two of 4 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: atomoxetine—*Strattera*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; fluvoxamine—*Luvoox*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor*

*See Reference Guide.

Predictors of Suicide After Self-Harm

In adolescents and young adults, risk of suicide was markedly elevated in the year following treatment for an episode of nonsuicidal self-injury. Risk was particularly high in males, American Indian and Alaskan Natives, and individuals who had used a violent method of self-harm.

Methods: The study was conducted to investigate the relative strengths of known risk factors for suicide, such as demographics, psychiatric disorders, and methods of self-harm, and to determine whether risk profiles differed between adolescents and young adults. Data were extracted from Medicaid records covering 45 states between 2001 and 2007. The cohort included patients, aged 12–24 years, with a clinical diagnosis of deliberate self-harm, who were followed for up to 1 year after receiving treatment for the injury. Study outcomes were repeated self-harm and death from suicide.

Results: A total of 32,395 initial nonfatal self-harm events were observed. About 17% of the patients had a second episode of self-harm during the follow-up year, with the maximum risk occurring in the first few days after the initial event. Adjusted risks of a repeat self-harm event were higher in females (hazard ratio* [HR], 1.33) and in American Indian and Alaskan Natives (HR, 1.18). A recent clinical diagnosis of ADHD was not associated with risk of repeated self-harm, but all other psychiatric diagnoses were, with particularly high risk in patients with personality (HR, 1.36) or anxiety disorders (HR, 1.24). Risk profiles did not differ substantially between adolescents (aged ≤17 years) and young adults.

During the 1-year follow-up, there were 48 completed suicides, 23 in adolescents and 25 in young adults. Mortality from suicide was nearly 27 times higher in this cohort than in the general U.S. population, matched for age, gender, and race and/or ethnicity. Adolescents with a history of self-injury were 46 times more likely than their peers in the general population to commit suicide, and young adults were 19 times more likely. After controlling for age and gender, the risk of suicide following self-harm was elevated in American Indian and Alaskan Natives (HR, 5.6), and individuals who had used a violent method (HR, 13.6), such as firearms (HR, 33.5), for their index episode of self-injury. Suicide risk was about 4-times higher in boys than in girls; however, they were significantly more likely to have used a

violent method during their initial self-harm event. Suicide rates were relatively low in African American and Hispanic individuals compared with whites, but these differences were not statistically significant.

Discussion: Nonfatal self-harm is strongly associated with both repeated nonfatal self-harm and suicide in the subsequent year, indicating the need for careful follow-up for all patients who self-harm. The present results suggest suicide prevention efforts may be especially necessary in males and those whose initial episode of self-harm was violent.

Olfson M, Wall M, Wang S, Crystal S, et al: Suicide after deliberate self-harm in adolescents and young adults. *Pediatrics* 2018; doi 10.1542/peds.2017-3517. From Columbia University, New York, NY; and other institutions. **Funded by the Agency for Healthcare Research and Quality. The authors declared no competing interests.**

*See Reference Guide.

Early Irritability and Suicide Risk

Irritability in childhood was predictive of increased risk of suicidal behaviors in adolescence in a population-based cohort study that used an innovative method of developmental-trajectory modeling.

Methods: The study cohort consisted of a representative sample of children born in the Canadian province of Quebec in 1997 and 1998 and followed through adolescence. At ages 6, 7, 8, 10, and 12 years, children were assessed by their teachers using the Behavior Questionnaire, a composite of items from several different standardized instruments. The questionnaire rated depressive/anxious mood with 9 items and irritability with 4 items. Serious suicidal ideation and suicide attempts were assessed by directly questioning study participants when they were aged 13, 15, and 17 years. Evaluation of developmental trajectories of irritability and depressive/anxious mood from ages 6–12 years resulted in 5 specific profiles: no irritability and low depressive/anxious mood; low irritability and low depressive/anxious mood; moderate irritability and low depressive/anxious mood; moderate declining irritability and high depressive/anxious mood; and high irritability and depressive/anxious mood. The 2 profiles with the lowest symptom levels and risk of adolescent suicidal behavior were merged and used as the reference group for estimation of odds ratios* and the number needed to be exposed* (NNE) for the other groups.

Results: The study included 1430 children who were followed through adolescence. More than half belonged to the 2 profiles with no or low irritability and low depressive/anxious mood. Members of the profile with the highest symptom levels were more likely than others to be male, from a socioeconomically advantaged family, and to be raised by a depressive and/or hostile-reactive mother.

Risk of suicidal behavior (serious ideation or attempt) during adolescence by childhood profile of irritability and depressed/anxious mood				
Profile		Subjects	Odds ratio for suicidal behavior [†]	NNE
Irritability	Depressed/anxious mood			
Moderate	Low	n=353 (25%)	1.51	48
Moderate declining	High	n=94 (7%)	0.96	-320
High	High	n=152 (11%)	2.22	18

[†]Adjusted for gender, socioeconomic status, and age

Overall rates of suicidal behavior ranged from 10.6 % (low irritability, high depressive/ anxious mood) to 16.4% (high on both traits). In an adjusted analysis, the odds of suicidal ideation and attempts were significantly elevated in adolescents who, as children, had high levels of irritability. The effect was particularly pronounced in girls. Moderate irritability plus low anxiety/ depression was also associated with a more modest increase in suicidal behavior, with a slightly larger impact in boys.

Discussion: Children with high irritability and depressive/ anxious mood and, to a lesser extent, those with moderate irritability appear to be at greater risk for suicidal behavior during adolescence compared with children with low symptom levels. However, in part because the scales used to assess symptoms in childhood were administered by teachers and were not clinical diagnostic instruments, the results must be viewed as preliminary and require replication before being used to create clinical screening recommendations.

Orri M, Galera C, Turecki G, Forte A, et al: Association of childhood irritability and depressive/ anxious mood profiles with adolescent suicidal ideation and attempts. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.0174. From the Institut National de la Sante et de la Recherche Medicale, Bordeaux, France; and other institutions. **Funded by the Quebec Government; and other sources. Five of 9 study authors disclosed potentially relevant relationships with noncommercial sources; the remaining authors declared no competing interests.**

*See Reference Guide.

OCD: Longitudinal Comorbidity

According to the results of a community-based cohort study, adolescents and young adults with obsessive-compulsive disorder are at increased risk for onset of other psychiatric disorders, particularly bipolar disorder and bulimia.

Background: There are several plausible mechanisms by which OCD could lead to subsequent mental-health disorders. Affective disorders could result from the demoralizing effects of obsessions and compulsions. Anxiety symptoms, already present in OCD, could progress into a clinical anxiety disorder, such as panic disorder or social phobia. Structural brain alterations in OCD could leave adolescents' brains more vulnerable to development of other disorders. Social discomfort because of obsessions and compulsions could put individuals with OCD at risk for social phobia. Cross-sectional relationships of OCD with other disorders have been observed in previous research. However, few studies have used longitudinal designs to evaluate the temporal relationship between OCD and subsequent development of other psychiatric disorders.

Methods: Data were collected from the Early Developmental Stages of Psychopathology study, a 10-year, prospective study from Munich, Germany. The study enrolled individuals who were aged 14–24 years at the 1995 baseline. Participants were assessed at entry and in 3 subsequent waves, with the last concluding 10.6 years after baseline. Mental health was measured using the Munich-Composite International-Diagnostic-Interview, a 2–3-hour face-to-face clinical interview assessing the presence of DSM-IV disorders. In addition to estimating the temporal relationship of OCD to other disorders, the investigators also estimated the attributable fraction and the population attributable fraction—i.e., the proportion of subsequent disorders that would not have occurred in the absence of OCD in persons identified with OCD and in the general population, respectively. These can provide a rough estimate of the potential impact of interventions to prevent OCD on the development of subsequent disorders.

Results: The analysis was based on 3021 study participants. At enrollment, 20 individuals (0.7%) met diagnostic criteria for OCD. By the end of follow-up, 55 persons (1.8%) met criteria for OCD. Nearly all patients with OCD had ≥ 1 comorbid psychiatric disorder.

After adjustment for age, gender, and other disorders occurring prior to OCD diagnosis, presence of OCD was significantly associated with later development of bipolar disorder, bulimia

nervosa, dysthymia, social phobia, and generalized anxiety disorder. (See table.) There was no association between OCD and later development of depression or substance use disorders. The highest attributable fractions in patients with OCD (>80%) were observed for bipolar disorder and bulimia, and attributable fractions were >65% for other disorders. At the population level, between 1.5% and 7.7% of the incidence of other disorders was attributable to prior OCD, assuming a causal relationship.

Discussion: The present data suggest that OCD can be conceptualized as a risk factor for other disorders. The large attributable fractions suggest that early treatment efforts in OCD could reduce the onset of many secondary mental disorders. Population attributable fractions were relatively low because of the low prevalence of OCD in the general population.

Association of OCD with later onset of other mental disorders	
Disorder	Hazard ratio*
Bipolar disorder	6.9
Bulimia nervosa	6.8
Dysthymia	4.4
Generalized anxiety disorder	3.4
Social phobia	2.9

Hofer P, Wahl K, Meyer A, Miche M, et al: Obsessive-compulsive disorder and the risk of subsequent mental disorders: a community study of adolescents and young adults. *Depression and Anxiety* 2018; doi 10.1002/da.22733. From the University of Basel, Switzerland; and other institutions. **Funded by the German Federal Ministry of Education and Research. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

ADHD-Related Time Management Deficits

In a randomized trial, a multimodal intervention improved time management skills in children and adolescents with ADHD.

Background: Time-related difficulties that interfere with daily routines, homework, school work, and social relations have been recognized in children with ADHD. However, the primary treatments for ADHD do not specifically address these time-related problems.

Methods: Study participants were families of children, aged 9–15 years, receiving treatment for ADHD. Despite pharmacotherapy, participating children had difficulties in daily time management, reported by parents on a structured questionnaire. The multimodal study intervention had 3 components: advocacy, compensation, and remediation. The advocacy component was delivered to all families and comprised a session with an occupational therapist to identify and prioritize the child's time management issues, followed by a 6-hour manualized, group education session for the parents and the child's coach. The lectures focused on deficits in time processing ability in ADHD, how to compensate, and how to support children with these deficiencies. In addition, the randomly selected intervention group received the compensation and remediation components. Compensation consisted of 3 or 4 sessions with both the parents and child, focusing on finding strategies to compensate for deficits, structuring the environment, and prescribing time-assisted devices such as alarms, schedules, or pictures. In the remediation component, the child performed 10 tasks from a series of up to 14 challenging time-skill training tasks of increasing complexity, with the support of a coach. The primary study outcome measures were the Kit for assessing time-processing ability (KaTid), the Time-Parent scale questionnaire, and the Time-Self-rating questionnaire. The interventions took place over 12 weeks, and outcomes were assessed after an additional 12 weeks of usual ADHD care.

Results: A total of 46 families were randomized, of which 38 completed the program and were evaluated at 24 weeks. Overall, time-processing ability improved in all children, but to a significantly greater degree in the group receiving the multimodal interventions (see table, next page), but effect sizes* were small. The KaTid time management subscale and self-reported daily time management improved comparably in the 2 groups.

Change from baseline in time-processing ability and daily time management in children receiving a multimodal intervention vs controls		
	Effect size	Significance
Time-processing ability (KaTid)		
Total score	0.38	p=0.019
Time perception subscale	0.29	p=0.046
Orientation to time subscale	0.42	p=0.01
Time management subscale	0.03	p=NS
Daily time management		
Time—Parent scale	1.0	p=0.011
Time—Self-report scale	-0.37	p=NS

Discussion: The 3 subscales of time-processing ability on the KaTid measure developmentally different ability levels, and the challenging tasks were also geared toward these levels. The children tended to complete lower-level challenges, related to time perception and time orientation, but may have not been sufficiently developmentally advanced to benefit from challenges to improve time management, the highest level. It is also not surprising that parents rated time management more highly than children, since the intervention may have made children more aware of their limitations.

Wennberg B, Janeslatt G, Kjellberg A, Gustafsson P: Effectiveness of time-related interventions in children with ADHD aged 9–15 years: a randomized controlled study. *European Child and Adolescent Psychiatry* 2018; doi 10.1007/s00787-017-1052-5. From Linköping University, Sweden; and other institutions. **Funded by the Medical Research Council of Southern Sweden; and other sources. The authors declared no competing interests.**

*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.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Number Needed to Be Exposed: A measure of how many patients need to have a specific risk factor to cause the outcome of interest in 1 patient. Lower NNE indicates more attributable risk.

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.

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.

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