Amphetamine Oral Suspension

The FDA has approved the first extended-release oral amphetamine suspension (Dyanavel XR) for use in children aged ≥6 years. The agent, developed using a patented LiquiXR™ technology, comprises both immediate- and extended-release amphetamine. The approval was based on a phase III, randomized, placebo-controlled, laboratory classroom study in 108 children, aged 6–12 years, with ADHD. The study included a 5-week, open-label, dose optimization phase, followed by a 1-week, double-blind treatment period. Participants demonstrated improvements in Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scores beginning 1 hour post dose and continuing through 13 hours. Nose bleed, allergic rhinitis, and upper abdominal pain were the most common adverse effects of treatment.

Dyanavel XR joins methylphenidate extended-release oral solution (Quillivant XR), approved in 2012, as the only available liquid stimulant preparations.

Brief CBT for Adolescent ADHD

A randomized trial found 2 relatively brief cognitive behavioral therapies improved ADHD symptoms, planning skills, and executive function in adolescents. Incorporating a specific focus on planning resulted in little additional benefit compared with solution-focused treatment that included no skills training.

**Background:** Executive-function deficits are common in adolescents with ADHD and often affect school and social functioning. While pharmacotherapy reduces core symptoms of ADHD, it does not generally affect executive function. CBT, aimed at these particular deficits, may be helpful, but most available programs are highly intensive, often consisting...
of 14–17 sessions or 5 months of twice-weekly sessions. The present study was undertaken to evaluate the efficacy of 2 shorter-term CBT interventions.

Methods: Study participants, aged 12–17 years, were recruited from 16 mental-health facilities in the Netherlands. For study inclusion, patients were required to have a confirmed ADHD diagnosis and to be enrolled in secondary school. Those who received any nonpharmacological treatment, including tutoring and remedial education, were excluded. Treatment consisted of 8 individual adolescent and 2 parent sessions, lasting 45–60 minutes each. Both treatments used motivational interviewing techniques, such as self-identified goals and collaborative treatment, to maximize autonomy and reduce attrition. The Plan My Life (PML) CBT taught a specific planning skill in each session (e.g., how to use to-do lists, prioritizing, dividing big problems into small steps, and concentration). The comparison treatment, named Solution-Focused Treatment (SFT) to make it appear as "credible" as PML, allowed the adolescent to choose a problem in each session and then receive guidance toward a solution, but it did not teach any planning skills. All participating therapists provided both treatments. The primary outcomes were parent-rated ADHD symptoms, planning skills, and executive function, measured using a combination of the Disruptive Behavior Disorders Rating Scale and the Behavior Rating Inventory of Executive Function.

Results: A total of 159 adolescents were randomly assigned to either PML (n=83) or SFT (n=76). They were representative of the ADHD population with regard to gender (74% boys), ADHD subtype (70% inattentive), and psychotropic medication use (78%). Only 4 patients in each group did not complete treatment.

Patients in both treatment groups showed considerable improvement from pretreatment to the follow-up assessment, conducted 3 months after completion of CBT. Treatment produced large, statistically significant effects on ADHD symptoms, executive function, and planning skills as well as comorbid anxiety and internalizing symptoms, with little difference in outcomes between the 2 treatments. There was a statistically nonsignificant trend toward larger improvement with PML in parent-rated executive function and planning. However, function was normal according to the Impairment Rating Scale, parent version, at follow-up in only 15% of the total sample of adolescents, compared with 6% at baseline.

Therapists reported they felt PML was better suited for adolescents with ADHD than SFT; parents also gave PML a more positive rating. Adolescents had no strong preference.

Discussion: The present study indicates relatively brief CBT may be beneficial and feasible in European and U.S. contexts. Arguably, the high proportion of participants who did not achieve normal function suggests more intensive treatment may be needed.

Boyer B, Geurts H, Prins P, Van der Oord S: Two novel CBTs for adolescents with ADHD: the value of planning skills. European Child and Adolescent Psychiatry 2015;24 (September):1075–1090. From the University of Amsterdam, the Netherlands. Funded by ZonMw, the Netherlands Organization for Health Research and Development. Two authors disclosed potential conflicts of interest; the remaining 2 authors declared no conflicts of interest.

Pediatric Mood Disorders and Atherosclerosis

Major depressive disorder and bipolar disorder confer moderately increased risk of accelerated atherosclerosis and early cardiovascular disease in children and adolescents, according to a Scientific Statement from the American Heart Association (AHA). Because pediatric mood disorders are highly prevalent and generally treatable, efforts to improve identification, monitoring, and treatment could result in substantial cardiovascular benefits.

Scientific evidence supports the addition of mood disorders to the short list of conditions that confer at least a moderate increase in cardiovascular risk (AHA "tier II" risk) in young patients.
The others, far less prevalent, are Kawasaki disease, chronic inflammatory disease, HIV, and nephrotic syndrome. These conditions are all associated with evidence of accelerated atherosclerosis before the age of 30 years. Studies that support the increased cardiovascular risk associated with pediatric mood disorders are few but convincing. Results of epidemiologic studies show increased risk of premature cardiovascular mortality and ischemic heart disease. Markers of elevated risk in young people with mood disorders include premature vascular aging (indicated by increased carotid intima-media thickness) and various indices of endothelial dysfunction.

The traditional cardiovascular risk factors of obesity, insulin resistance, and dyslipidemia have increased prevalence in young people with mood disorders. They also have disproportionate exposure to behavioral and environmental factors contributing to risk, including early mistreatment; sleep disturbance; poor nutrition; sedentary lifestyle; smoking; and alcohol and illicit-substance use. Second-generation antipsychotics, and to a lesser extent antidepressants and mood stabilizing drugs, are associated with weight gain and other adverse metabolic changes. However, direct evidence linking these drugs with cardiovascular disease is lacking, and risk has been shown to be elevated even in young people not exposed to these medications.

Treatment guidelines for cardiovascular risk reduction specific to young people with major depressive disorder or bipolar disorder are not yet available. Current guidelines for managing mood disorders do not adequately address cardiovascular risk factors in youth with depression or the importance of metabolic monitoring, even in patients with unmedicated bipolar disorder. Goldstein B, Carnethon M, Mathews K, McIntyre R, et al: Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a Scientific Statement from the American Heart Association. Circulation 2015; doi 10.1161/CIR.0000000000000229. From the American Heart Association. Two study authors disclosed financial relationships with commercial sources; the remaining 11 authors declared no competing interests.

**Targeted Prevention of Anxiety Disorders**

A brief family-based cognitive behavioral intervention reduced the onset of anxiety disorders in a group of at-risk children.

**Background:** Offspring of parents with anxiety are vulnerable to development of anxiety disorders themselves. Untreated anxiety in young patients can lead to adverse academic and social outcomes, yet many young people with anxiety receive no treatment. Practical preventive or early intervention programs are needed for these at-risk youths.

**Methods:** Participating families were recruited from the community or referred by clinicians. Families were required to have ≥1 parent with a current anxiety disorder and a child, aged 6–13 years, who did not have an anxiety disorder. The parent and child were the study subjects, but other family members were invited to participate in the therapy. The active intervention was the manualized Coping and Promoting Strength program, consisting of 8 weekly 60-minute sessions and 3 optional booster sessions. The program focused on cognitive techniques to address modifiable child and parent risk factors for anxiety disorders. A comparison group received only a pamphlet with information about anxiety disorders and their treatments, without revealing the anxiety-reduction strategies taught in the active program. The control intervention was designed to represent the type of treatment these children would receive under ordinary conditions. The primary study outcome was the onset of a child anxiety disorder over 12 months of follow-up. Anxiety in children was rated using the Anxiety Disorders Interview Schedule.

**Results:** A total of 70 families received the Coping and Promoting Strength program, and 66 received the pamphlets. About half of the recruited children (in both groups) had significant
subclinical anxiety symptoms; only a few children had non-anxiety disorders (i.e., ADHD and enuresis). Families in the active intervention group attended an average of 9 of the 11 available sessions. The parents with the anxiety disorders attended all sessions, and the other parents were also present in half.

Anxiety disorders in the children were assessed at the completion of treatment and after 6 and 12 months. At the post-intervention assessment, anxiety disorders were present in 5 of the control subjects, compared with none of the active-treatment subjects. Over the course of the year, anxiety disorders were present in 19 and 3 patients in the groups, respectively (odds ratio,* 8.54; p<0.001). The number needed to treat* to prevent an anxiety disorder diagnosis at 1 year was 4. At all time intervals, anxiety symptom severity was significantly lower in children who participated in the program, with effect sizes* of 0.74 posttreatment and 0.62 at 12 months. According to parent reports, use of mental health services for child anxiety was lower in the group receiving treatment, although the difference was not statistically significant (22% vs. 13%).

Discussion: Most studies of anxiety disorder prevention in children have been only modestly effective and have been conducted in schools as universal prevention efforts. No program in the U.S. has previously targeted high-risk offspring of anxious parents. The targeted program described in this study was associated with larger effect sizes than those typically associated with universal prevention programs. Exploration of several theory-driven mediators of treatment effects suggests that the program worked by reducing parental modeling of anxiety and global distress, which reduced child anxiety symptoms.


*See Reference Guide.

Childhood Abuse and Neurofunctional Abnormalities

Functional MRI (fMRI) studies showed slower error processing and increased activation of brain regions involved in error processing in young people with a history of severe physical abuse, compared with both psychiatric and healthy controls. These differences may arise from the need of abused children to constantly monitor their actions to avoid punishment.

Background: Deficits in cognitive control have been reported in patients with a history of childhood abuse or maltreatment. Ability to correctly detect errors and adjust behavior accordingly may be particularly important in abusive settings where punishment for mistakes is often harsh. However, research has suggested that persistent harsh punishments may sensitize a child to errors and lead to an overactive error-monitoring system.

Methods: Study participants were 22 medication-free young people, aged 13–20 years, referred from social services or psychiatric clinics. These patients had a history of severe childhood abuse, as determined by the Childhood Trauma Questionnaire and reports from the referring agency. Those with a history of sexual abuse were excluded because that type of abuse has different effects on brain structure and function. The study also included 2 comparison groups: 27 healthy control subjects from a similar socioeconomic background, and 17 young people with similar psychiatric comorbidity, including PTSD from non-abuse-related trauma. fMRI data were acquired during the stop task, in which the subject inhibits motor responses to go signals followed by unpredictably timed stop signals. The test was designed to elicit errors 50% of the time.
Results: Study participants had a mean age of 17 years. Those with a history of abuse had a somewhat lower IQ than both comparison groups, as expected because they had suffered the known cognitive consequences of their abuse. PTSD was present in 13 patients who had experienced abuse and in 12 psychiatric controls; depression and anxiety were also common in these groups.

Participants with a history of abuse had significantly slower responses on both go-signal reaction time and post-error reaction time than healthy controls (p<0.05). For failed inhibition trials, compared with healthy controls, abused young people also had significantly increased activation of error-processing regions of the dorsomedial frontal cortex, a large cluster comprising the left and right pre-supplementary and supplementary motor area, dorsal anterior cingulate cortex, and superior frontal gyri, as well as the left paracentral lobule. Compared with psychiatric controls, the abused subjects had increased activation in a smaller cluster in the supplementary motor area. Patterns of brain activation did not differ between the 2 control groups. The 3 groups did not differ in brain activation following successful trials, which suggests the functional abnormalities were specific to error processing. The results were robust in additional analyses that were conducted separately to adjust for IQ, psychopathology, and demographic factors.


Antidepressant Study Flawed

An independent reanalysis of data from an industry-sponsored controlled trial of paroxetine in adolescent depression has overturned the trial's major conclusion of efficacy and revealed higher-than-reported rates of serious adverse effects.1

Background: The trial data, published 14 years ago, were reanalyzed as part of the "restoring invisible and abandoned trials" (RIAT) initiative, started by an international group of researchers who believe there is a need to correct misleading reporting. RIAT researchers identified Study 329 as a misreported trial in need of restoration. The study, which claimed superior efficacy of paroxetine and imipramine compared with placebo, was conducted by SmithKline Beecham and published in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 2001.2

Methods: For the reanalysis, the RIAT investigators used data from the clinical study publicly available on the manufacturer's website, other publicly available documents, and individual participant data provided by the manufacturer on a private website. The data were reanalyzed, for the most part using methods set out in the original study protocol. The study recruited 275 adolescents, aged 12–18 years, with DSM-III-R major depression of ≥8 weeks' duration. Patients were randomly assigned to receive flexibly-dosed paroxetine, imipramine, or placebo for 8 weeks. The study had 2 primary efficacy outcomes: change from baseline in the Hamilton Rating Scale for Depression (HAM-D) total score; and response, defined as a ≥50% reduction in the HAM-D or a score of ≤8.

Results: The protocol-specified analysis plan called for computation of an omnibus statistic for the overall significance of results for the 2 primary outcomes in all 3 treatment groups, followed by pairwise testing between treatments only if the omnibus statistic was significant. The RIAT investigators found that the omnibus statistic was not significant—there was no difference among the effects of 2 antidepressants and placebo—therefore, pairwise comparisons were not warranted. In the original publication and the clinical study report, the investigators did not
report the omnibus statistic but analyzed 2 of the 3 possible pairwise comparisons, finding significant differences between paroxetine and placebo and between imipramine and placebo. The original investigators set a prespecified threshold of 4 HAM-D points as signaling a clinically significant difference between treatments. The mean HAM-D decreased by 10.7 points with paroxetine, 9.0 with imipramine, and 9.1 with placebo.

The RIAT investigators also found no difference among treatments for any of the protocol-specified secondary endpoints. The original investigators found significant differences between treatments for 4 outcome variables that were not specified in the original analysis plan.

Significant underreporting of adverse events was also found in the re-analysis. Data from the patient-level forms were simply not transcribed into the adverse event listings in the clinical study report or were miscoded, resulting in underreporting of "serious, severe, and suicidal adverse events," the RIAT investigators say.

**Editorial.** Few studies have received as much criticism as Study 329. It was deemed a "failed trial" by an FDA reviewer, yet used aggressively in the marketing of paroxetine. Failure to retract the publication has been attributed to the journal, the manufacturer, the American Academy of Child & Adolescent Psychiatry—whose ethics committee lacks a mandate to investigate misconduct, and Brown University—the principal research institution.

1 Le Noury J, Nardo J, Healy D, Jureidini J, et al: Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. BMJ 2015; doi 10.1136/bmj.h4320. From Bangor University, Wales, U.K.; and other institutions. The Original Study 329 was funded by SmithKline Beecham. The reanalysis was conducted without specific funding. Some of the authors reported potential conflicts of interest.
3 Doshi P: No correction, no retraction, no apology, no comment: paroxetine trial reanalysis raises questions about institutional responsibility (Feature). BMJ 2015; doi 10.1136/bmj.h4629. The author is an associate editor of BMJ.

**Drug Trade Names:** imipramine—Tofranil; paroxetine—Paxil

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**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.

**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.

**Number Needed to Treat:** Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.