Novel Treatments for Attention-Deficit/Hyperactivity Disorder in Children

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Optimal medications for children with attention-deficit/hyperactivity disorder (ADHD) would be effective, well tolerated, and long acting and not cause mood swings or worsen comorbid conditions. Current medications work on brain dopamine and/or norepinephrine systems, which are thought to be involved in ADHD. The medication class with the most evidence of efficacy in ADHD is stimulants, but they may be abused, are effective for only 4 to 12 hours, and may cause mood swings or increase tic severity. In recent years, alternative treatments have been explored. Tricyclic antidepressants have efficacy comparable to that of stimulants but may cause constipation, dry mouth, tremors, blood pressure changes, and potentially serious side effects including cardiac conduction and repolarization delays. Monoamine oxidase inhibitors may improve ADHD symptoms but are associated with severe dietary restrictions. Serotonin reuptake inhibitors have little or no effect in ADHD but may improve comorbid depression. Bupropion, although less effective than stimulants, may improve both ADHD symptoms and comorbid depression. Antihypertensive agents may improve impulsivity, hyperactivity, and comorbid tics but cause sedation or rebound hypertension. Atomoxetine, which is being developed for ADHD, reduces symptoms of ADHD without exacerbating comorbid conditions and is associated with only minor side effects, including subtle changes in blood pressure and heart rate. Before prescribing a treatment, physicians should consider the appropriateness and effectiveness of any medication for children with ADHD, who may be less tolerant of side effects and less able to monitor and express concerns about their well-being than adults.

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The first-line treatment for children with attention-deficit/hyperactivity disorder (ADHD) has traditionally been stimulants. However, some children are unresponsive to stimulants or intolerant of their side effects. Other medications, such as antidepressants and antihypertensives, that have been tried in ADHD were originally developed for other disorders. These medications tend to have side effects related to their mechanism of action and be less effective than stimulants in treating ADHD. As more is understood about this illness, newer medications are being tested in ADHD. Therefore, clinicians need to reexamine the appropriateness and effectiveness of all medications used for ADHD in children, who may be less tolerant of side effects and less able to monitor and express concerns about their well-being than adults.

THE OPTIMAL PROFILE FOR EFFECTIVE MEDICATIONS FOR CHILDREN WITH ADHD

There are a number of considerations to examine in considering an optimal medication candidate for children with ADHD. Optimally, medications for ADHD should be long acting. ADHD potentially affects every aspect of an individual's life, including impulse control, hygiene, driving, sleeping, thinking, and social functioning throughout the entire day. Currently, the longest acting stimulant medications last 12 hours, leaving a child untreated during evening and early morning hours. When the effects of medication have worn off, children may be hyperactive or irritable. Also, getting children to take medication can be difficult, especially in front of their peers at school. Medications that are taken only once per day could increase children's compliance and eliminate the need for students to receive a dose of medication at school. When choosing a medication, clinicians should also consider potential side effects as well as comorbid conditions. Many children with ADHD have comorbid conditions such as tics, depression, and anxiety,[1] which could be exacerbated by current ADHD medications. In addition, medications that may potentially be abused may be problematic.

Currently, medications that effectively treat ADHD target the dopamine and norepinephrine systems, which are thought to be involved in the etiology of ADHD. Dopamine and norepinephrine are catecholamines with nearly identical structures; norepinephrine has an additional hydroxyl group. These 2 catecholamines interact with each other. However, these catecholamines have pharmacologically unique distribution and regulatory systems. Norepinephrine is involved in a number of cognitive functions including signal processing.

The source of most of the norepinephrine in the central nervous system is the locus ceruleus, which has been shown to induce a waking alert state and to enhance informational processing and attention to environmental stimuli.[2] When the locus ceruleus releases norepinephrine into the cortex, postsynaptic firing decreases, and the cortex becomes more receptive to afferent signals. This change in processing occurs throughout the brain, affecting many synapses at once.[3,4]

Adequate levels of norepinephrine and dopamine are necessary for the optimal function of the prefrontal cortex in the monkey.[5] Some of the findings in the model of executive functions and neurotransmitter innervation in the monkey brain may apply to ADHD in humans.[3] Arnsten and colleagues[5] proposed a model of ADHD in which low amounts of norepinephrine may be inadequate for cognitive functioning of the prefrontal cortex. Deficits in the right dorsal prefrontal cortex have been shown to affect attention regulation and inhibition response to distracting stimuli, and deficits in the right orbital prefrontal cortex are associated with immature behavior, lack of restraint, and increased motor activity. The opposite occurrence, the release of high levels of catecholamines, may also disrupt cognitive function and account for features of disorders such as posttraumatic stress disorder. Arnsten et al.[5] found that α_2-adrenergic agonists, i.e., clonidine and guanfacine, improved some cognitive functions in primates. However, in clinical populations, cognitive improvement has not been clearly shown.

The dorsal lateral prefrontal cortex is related to working memory, which is the ability to access and manipulate information. Working memory uses internal representations to regulate behavior and compare incoming information with the memory of previous stimuli. Barkley[6] developed a model of executive dysfunctions located in the prefrontal cortex in the phenotype of ADHD, which fits with Arnsten's nonhuman primate model, in which deficits in behavioral inhibition; working memory; self-regulation of affect, motivation, and arousal; and the ability to analyze and synthesize behavior underlie ADHD. This model of ADHD shifts the focus from directly correcting bad behavior to improving underlying cognitive deficits.

This neurobiological perspective is supported by genetic studies of ADHD. The gene candidates for ADHD include the dopamine transporter gene (*DAT*) and the D$_4$ dopamine receptor gene (*DRD4*).[7] *DRD4* responds to not only dopamine but also norepinephrine; therefore, medications that affect norepinephrine may work by triggering the dopamine system in the cortex. These genetic findings and models of dysfunctions fit with current neuropsychological, imaging, and pharmacologic data emerging in ADHD research and provide compelling support for the role of norepinephrine in ADHD.

EFFICACY AND SAFETY OF MEDICATIONS STUDIED IN CHILDREN AND ADOLESCENTS WITH ADHD

Stimulants

The first-line treatment for ADHD is stimulants, such as methylphenidate, dextroamphetamine, and the combination of amphetamine and dextroamphetamine. About 70% of patients with ADHD who take a stimulant medication will experience improvement in their core symptoms.[8] This therapeutic benefit may be the result of stimulants' affecting dopamine and norepinephrine levels in the central nervous system.[9] Although stimulants have been shown to be generally safe,[10] not all patients respond to these drugs. As a class, these drugs have common side effects such as weight loss, stomachaches, headaches, and initial insomnia, and, less commonly, irritability.[10] Stimulants may also raise blood pressure and pulse, and induce or exacerbate tics. Pemoline is not a first-line stimulant treatment for ADHD because it has been associated with rare but potentially life-threatening hepatoxicity.[11]

Tricyclic Antidepressants

Of the nonstimulant medications used in ADHD, tricyclic antidepressants (TCAs) are the most studied, possibly because they have been in existence longer than most other candidate medications and have been shown to be effective in this disorder. TCAs such as imipramine and desipramine have been studied in ADHD because they inhibit norepinephrine reuptake.[12] The TCAs shown to have the greatest effect in ADHD—comparable even to the efficacy of the stimulants—are desipramine and imipramine. Most studies of the effectiveness of imipramine in this disorder used the criteria of hyperactivity or *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, (DSM-III) attention deficit disorder (ADD) and were conducted more than 20 years ago. Both open[13,14] and controlled trials[15,16] have shown that at doses as low as 75 mg/day, imipramine may begin to reduce hyperactivity in 3 to 10 days.

In the 1980s, small, open trials[17,18] demonstrated the effectiveness of desipramine in DSM-III ADD. Biederman and colleagues[19] reported the results of the largest controlled trial of desipramine in ADD in 1989. Sixty-two children and adolescents with DSM-III attention deficit disorder with hyperactivity (ADD-H) were randomly

assigned to treatment with desipramine or placebo. About 70% of the 31 patients treated with 4.6 mg/kg of desipramine had a statistically significant (p = .0001) response, a rate comparable to that found in studies of stimulants. The effect of desipramine seemed to be independent of the effects of stimulants because 69% of the study participants had previously failed to respond to or poorly tolerated stimulants. In further analysis,[20] desipramine was found to be as effective in the patients who had a history of depression as in those without such a history. Recently, my colleagues and I[21] conducted a 6-week double-blind, placebo-controlled trial of desipramine in 41 children and adolescents with chronic tic disorders including Tourette's disorder and DSM-IV ADHD. Desipramine lowered patients' scores on both the DSM-IV ADHD Symptoms Checklist and the Yale Global Tic Severity Scale. This reduction in tics was similar to the reduction seen with guanfacine.[22]

Although some TCAs are effective in ADHD, their use in children has declined because of their possible cardiac side effects and associated monitoring. Mild side effects include dry mouth, constipation, sedation, and weight gain. Because TCAs affect cardiac conduction and repolarization, physicians must clearly explain to families the risk of death associated with overdose. Desipramine has also been associated with a rare incidence of sudden death of unexplained origin, possibly related to lengthening of the QT interval. Therefore, to use these medications, prescribing clinicians must carefully watch symptoms referable to the cardiovascular system and obtain periodic electrocardiograms and blood drug levels.

Monoamine Oxidase Inhibitors

The few studies of monoamine oxidase inhibitors (MAOIs) in children with ADHD have generally found these drugs to reduce the severity of symptoms. In a 1985 double-blind, crossover study[23] that compared dextroamphetamine with either clorgyline, which is no longer available, or tranylcypromine in 14 boys with DSM-III ADD-H, all 3 drugs substantially reduced scores on the Conners Abbreviated Teacher Rating Scale, 48-Item Parent Questionnaire, and a modified version of the Continuous Performance Test. Moclobemide, an MAOI that is not available in the United States, was also effective in reducing the symptoms of ADHD in 2 studies[24,25] of 12 to 15 children between the ages of 6 and 13. Selegiline (L-deprenyl) has been studied in children with both ADHD and Tourette's disorder. In an open trial,[26] 26 of the 29 children who were enrolled in the study experienced substantial improvement in their ADHD symptoms, and the tics of only 2 children worsened. Although the improvement in ADHD Rating Scale-IV scores was not significant in a double-blind, placebo-controlled, crossover study[27] of 24 children, the improvement in Yale Global Tic Severity Scale scores was substantial.

The action of MAOIs in reducing ADHD symptom severity is probably related to their ability to block the metabolism of norepinephrine and dopamine.[12] Despite their effectiveness, MAOIs are rarely prescribed for children with ADHD because these agents have severe dietary restrictions.

Selective Serotonin Reuptake Inhibitors

The effects of selective serotonin reuptake inhibitors (SSRIs) on ADHD have been studied in only small open trials. In a 6-week open trial, Barrickman et al.[28] examined the efficacy of fluoxetine in 19 children with DSM-III-R ADHD. About 60% of these patients experienced some improvement in ADHD symptoms. However, in a clinical case series[29] of fluoxetine or sertraline monotherapy in 7 adolescents and 4 adults with major depression and ADHD, no patient's ADHD symptoms improved. When stimulants were added to the patients' therapy, their ADHD symptoms improved, and the SSRIs continued to reduce symptoms of depression. While it is doubtful that SSRIs are effective in ADHD, these medications may be helpful with comorbid depression and appear to be generally safe in combination with stimulant therapy.[29]

Bupropion

Several trials of bupropion have shown efficacy in children with ADHD. In a multicenter, double-blind, placebo-controlled trial[30] of 109 children with DSM-III ADD-H, significant improvements were found in scores on the Conners Parent and Teachers Questionnaires, the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement scales, and the Continuous Performance Test with bupropion treatment. In a trial[31] comparing bupropion with methylphenidate, which used a double-blind crossover design, significant (p < .001) improvements were found in scores on the parent- and teacher-completed IOWA Conners Teacher's Rating Scale with both bupropion and methylphenidate treatment.

Bupropion has also been found to be effective in children and adolescents with comorbid psychiatric disorders. An open trial of 24 adolescents showed that bupropion was effective in both depression and ADHD for 58% of the subjects.[32] In a 5-week, open trial[33] in 13 male adolescents with ADHD and comorbid substance abuse and conduct disorders, bupropion significantly reduced scores on the Conners Hyperactivity Index (p < .01) and Daydream Attention (p < .02) subscales and the CGI-S (p < .002) rating scale.

Despite the positive results from clinical trials, improvement in ADHD with bupropion is generally not as complete as improvement with stimulants.[34]

Antihypertensives

Antihypertensives, such as clonidine and guanfacine, that are α_2-adrenergic agonists, have been effective in

reducing some ADHD symptoms in children.[22,35–38] In a 3-month, randomized, blinded, group comparison, Connor et al.[37] studied clonidine monotherapy, methylphenidate monotherapy, and clonidine and methylphenidate combination therapy in 24 children with ADHD and aggressive oppositional defiant disorder or conduct disorder. Scores on parent-rated and teacher-rated scales of attention, hyperactivity, oppositional behavior, and conduct improved significantly in each of the 3 treatment groups. In an open trial of guanfacine in 13 children with ADHD, Hunt and colleagues[36] found that patients' mean overall scores on the Conners Parent Rating Scale improved significantly (p < .015), as did their scores on inattention, hyperactivity, and immaturity subscales (p < .01). Guanfacine may also improve comorbid tic disorders. In an 8-week, randomized, placebo-controlled trial of 34 children with both DSM-IV ADHD and tic disorders, Scahill and colleagues[22] found mean reductions of 37% in teacher-rated ADHD Rating Scale-IV scores and 31% in Yale Global Tic Severity Scale scores.
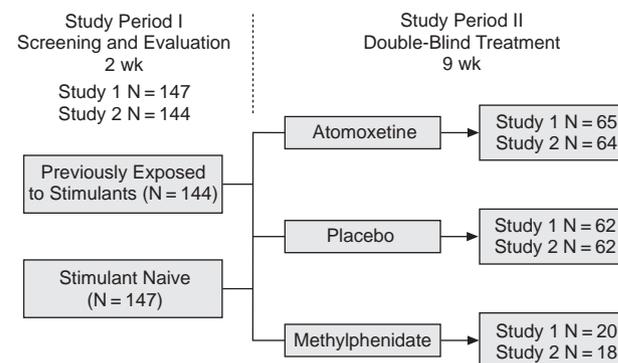
These α_2-adrenergic agonists may work in ADHD by affecting norepinephrine discharge rates in the locus ceruleus, and this action may indirectly affect dopamine firing rates.[39] Although effective in ADHD, clonidine and, to a lesser extent, guanfacine may be associated with rebound hypertension and sedation. However, in a systematic chart review of 62 children and adolescents, Prince et al.[40] found that the sedative effect of clonidine improved sleep disturbances associated with ADHD, as measured by the National Institute of Mental Health global assessment of improvement.

Atomoxetine

Recently, a novel compound, atomoxetine, has shown promise in ADHD. Atomoxetine is a specific, potent norepinephrine reuptake inhibitor similar in structure to fluoxetine although not fluorinated. This medication, which was formerly known as tomoxetine, has not yet been approved by the U.S. Food and Drug Administration for ADHD. Initial open studies of atomoxetine showed that this medication may be effective in reducing ADHD symptoms and, because of its selectivity, well tolerated in children and adolescents.

To determine the safety, efficacy, and range of therapeutic dose of atomoxetine in children, my colleagues and I[41] conducted an 11-week, open study of atomoxetine at doses between 10 and 90 mg/day in 30 children with DSM-IV ADHD who were 7 to 14 years old. Atomoxetine significantly (p < .001) reduced scores on the ADHD Rating Scale-IV inattention and hyperactivity/impulsivity subscales. Significant (p < .001) improvements were also found in scores on the CGI-S for ADHD and the cognitive problems and hyperactivity subscales and ADHD Index of the Conners Parent Rating Scale-Revised, Short Form. Over 75% of subjects who completed 10 weeks of treat-

Figure 1. Design of 2 Placebo-Controlled Trials of Atomoxetine Treatment in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder[a]

[a]Data from Spencer et al.[42]
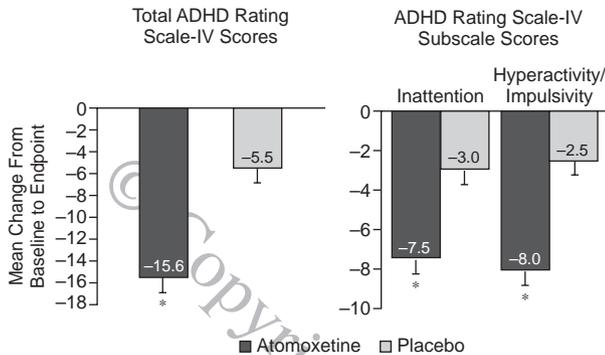*p < .001 vs. placebo.

ment showed > 25% decrease in ADHD symptoms. Adverse effects were mild and transient, and atomoxetine was also associated with subtle but statistically significant increases in heart rate (p < .01) and diastolic blood pressure (p < .001).

On the basis of these promising open data, a series of large controlled trials was initiated. In the first trials,[42] a total of 291 children between the ages of 7 and 13 who had ADHD were assigned to either of 2 large, randomized, placebo-controlled trials of acute treatment with atomoxetine at 17 sites in the United States (Figure 1). To be included, subjects had to meet DSM-IV criteria for ADHD and have at least a 1.5 standard deviation above the normative scores for their age and gender on the ADHD Rating Scale-IV. Subjects could have comorbid conditions such as anxiety, depression, conduct disorder, and oppositional defiant disorder, but subjects with bipolar or tic disorders were excluded. About half of the subjects were stimulant naive, and some of these stimulant-naive subjects were randomly assigned to methylphenidate instead of atomoxetine or placebo to validate study methodology. That is, if the group randomly assigned to methylphenidate showed little or no improvement, this result would indicate that the study methodology was flawed.
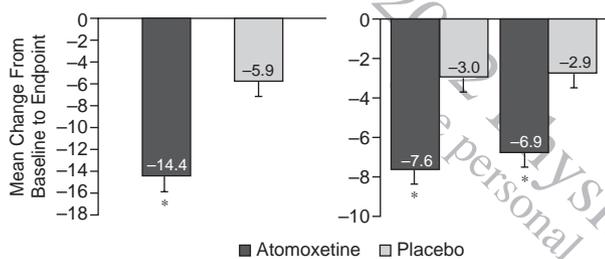
In both studies, improvements in total ADHD Rating Scale-IV scores and inattention and hyperactivity/impulsivity subscale scores were significantly greater (p < .001) with atomoxetine than placebo (Figure 2). In addition, the improvement with atomoxetine was similar for both inattention and hyperactivity/impulsivity. In the 143 subjects who were stimulant naive, both atomoxetine and methylphenidate separated significantly (p < .001) from placebo. The mean doses of atomoxetine and methylphenidate were 1.5 mg/kg and 1 mg/kg, respectively, divided into 2 doses per day. Although the improvement in

Figure 2. Changes in Attention-Deficit/Hyperactivity Disorder (ADHD) Rating Scale-IV Scores for Children Treated With Atomoxetine or Placebo[a]
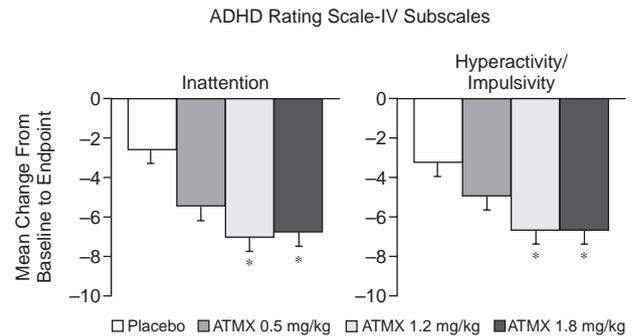

Study 1

Study 2

[a]Data from Spencer et al.[42]
*p < .001 vs. placebo.

Figure 3. Changes in Attention-Deficit/Hyperactivity Disorder (ADHD) Rating Scale-IV Subscale Scores for Children and Adolescents Treated With Atomoxetine (ATMX) or Placebo[a]

[a]Data from Michelson et al.[43] Test for linear dose response was significant at p < .001 for both subscales.
*p < .001 vs. placebo.

After the initial 2 randomized, placebo-controlled trials were conducted, Michelson and colleagues[43] studied 3 different doses—0.5 mg/kg, 1.2 mg/kg, and 1.8 mg/kg per day—of atomoxetine in an 8-week, randomized, placebo-controlled trial of 297 individuals who were between 8 and 18 years old. Before being randomly assigned to 1 of the 3 doses of atomoxetine or to placebo, subjects were evaluated and then discontinued other medications. Outcome measures were expanded from previous studies to include improvement in not only ADHD symptoms but also affective symptoms and social and family function.

The improvement in the total ADHD Rating Scale-IV scores was substantially greater for the 0.5-mg/kg dose of atomoxetine than placebo but even greater for the 1.2-mg/kg and 1.8-mg/kg doses of atomoxetine (p < .001) compared with placebo. A similar effect was seen in the change in inattention and hyperactivity/impulsivity subscale scores (Figure 3). Atomoxetine was also associated with improvements in oppositional behavior and depression. Findings from the Conners Parent Rating Scale showed that all 3 doses of atomoxetine were also significantly more effective than placebo in reducing oppositional behavior—p < .05 for the 0.5-mg/kg dose and p < .01 for the 1.2-mg/kg and 1.8-mg/kg doses. Although only one of the subjects in this study had major depressive disorder, the 2 higher doses of atomoxetine were significantly (p < .05) more effective than placebo in reducing scores on the revised Children's Depression Rating Scale.

According to analyses of parents' responses to the Child Health Questionnaire, atomoxetine had a positive effect on both the subjects' and parents' well-being. For the child-related measures, all 3 doses of atomoxetine separated significantly from placebo on the psychosocial measure, and the 1.2-mg/kg dose also separated significantly from placebo on the self-esteem measure. For the parent-related measures, only the 1.8-mg/kg dose was

ADHD Rating Scale-IV scores was slightly lower with atomoxetine than methylphenidate, the magnitude of the change with both drugs was comparable.

Data on adverse events were available for 280 of the 291 subjects (129 in the atomoxetine group, 124 in the placebo group, and 37 in the methylphenidate group). The most common adverse events included headache, abdominal pain, nausea, and emotional lability, none of which were significantly more common in patients taking atomoxetine than those taking placebo. A significantly higher percentage of patients treated with atomoxetine than placebo reported treatment-emergent decreased appetite (22% vs. 7%, respectively; p < .05). However, decreased appetite was also common in the methylphenidate group, in which 12 subjects (32%) experienced this adverse event. Only 9 subjects (7.0%) treated with atomoxetine experienced insomnia, a lower rate of occurrence than in either the placebo group, in which 11 subjects (8.9%) experienced this event, or the methylphenidate group, in which 10 subjects (27.0%) experienced this event. In addition, there were no significant changes in laboratory values or cardiac function associated with atomoxetine treatment.

significantly (p < .05) more effective in reducing the impact of their children's ADHD on the parents' emotions and time demands. The long-term extension of this 8-week study will continue to examine effects of atomoxetine on both the deficits associated with ADHD and comorbid conditions.

CONCLUSION

Studies of medication treatment in children with ADHD have shown that the drugs that are most effective—stimulants, TCAs, and atomoxetine—target dopamine and/or norepinephrine receptors. Although stimulants have the most evidence of efficacy in ADHD, they are not always effective and require repeated dosing throughout the day. Although TCAs may have an effect comparable to that of stimulants in ADHD, nuisance side effects and cardiac issues complicate their use in children. Therefore, new treatments such as atomoxetine that are effective, well tolerated, and selective in their action will provide new options for children with ADHD.

Drug names: amphetamine and dextroamphetamine (Adderall), bupropion (Wellbutrin and others), clonidine (Catapres, Duraclon, and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine, Dextrostat, and others), fluoxetine (Prozac and others), guanfacine (Tenex and others), imipramine (Tofranil and others), methylphenidate (Concerta, Methylin, and others), pemoline (Cylert and others), selegiline (Eldepryl and others), sertraline (Zoloft), tranylcypromine (Parnate).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, bupropion, clonidine, desipramine, guanfacine, imipramine, selegiline, tranylcypromine, atomoxetine, clorgyline, and moclobemide are not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder.

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