Effects of Atomoxetine and Methylphenidate on Sleep in Children with Attention-Deficit/Hyperactivity Disorder

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Attention-deficit/hyperactivity disorder (ADHD) affects approximately 3% to 7% of school-aged children. It is characterized by inattention and/or hyperactivity and impulsivity. The disorder is thought to be caused by a dysregulation of norepinephrine and dopamine in the prefrontal cortex and associated brain structures.

Therapy for ADHD, which has traditionally relied on the administration of stimulants, does not produce an adequate response or is not tolerated in 30% or more of patients. In a 1999 survey, 61% of children with ADHD who took stimulant medications experienced insomnia at least one night per week, compared with 32% of children with ADHD who did not take stimulants.1

Atomoxetine (ATX) (Strattera®, Eli Lilly) is a highly specific, presynaptic inhibitor of the norepinephrine transporter. It is indicated for ADHD in children, adolescents, and adults.

In a randomized, double-blind, crossover trial of 85 children with ADHD, as defined in the Diagnostic and Statistical Manual, fourth revised edition (DSM-IV), investigators compared ATX twice daily with methylphenidate (MPH) three times daily to determine whether ATX, because it is not a stimulant, interferes with sleep less than MPH does. The children ranged in age from six to 14 years, and 24.7% were girls.

Two treatment periods of 6.7 weeks were separated by a 10- to 20-day drug-free interval. Actigraphy (a wrist monitor), polysomnography (at two sites), and diaries kept by parents and children were used to assess the outcomes. Subjects agreed to refrain from consuming caffeinated beverages and to maintain a consistent “lights out” bedtime; the participants were excluded for less than 85% adherence.

The mean final doses were 1.56 mg/kg per day for ATX and 1.12 mg/kg per day for MPH. In relation to the baseline values, there was a significant ($P < .001$) increase in the time to sleep onset with MPH (3.4 minutes), compared with ATX (30.1 minutes). As evaluated by actigraphy, the actual total sleep time favored ATX.

For 39 patients who were assessed via polysomnography, the time to the first sleep episode was significantly less with ATX (~0.3 minutes vs. 16.8 minutes, both from baseline; $P < .001$). The same pattern from baseline was revealed in the time to the first persistent sleep (~0.2 minutes vs. 16.8 minutes), but the number of awakenings favored MPH (~4.4 vs. ~6.7; $P = .002$).

In the children’s diaries, responses to questions (time to falling asleep, difficulty getting up, how well did you sleep? how sleepy do you feel today?) all favored ATX, significantly for the first three items.

Parent diary results favored ATX for difficulty in getting the child out of bed, difficulty with getting the child ready for bed, arguing or struggling in the morning, irritability in the morning, difficulty in getting ready for bed, and difficulty with falling asleep. MPH was not favored in any category. Both ATX and MPH were well tolerated in this patient population.

Overall, patients taking ATX experienced a shorter time to the onset of sleep, compared with MPH, as measured by actigraphy and polysomnography. Patients taking MPH had less actual sleep time, as assessed by actigraphy, and more sleep-related problems, according to both child and parent diaries.

A limitation of this study was that polysomnography was performed in only a subset of patients.

Duloxetine Versus Placebo in Preventing Relapse of Major Depressive Disorder

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It has been well established for more than a decade that major depressive disorder (MDD) is characterized by several distinct stages:2

- an acute phase for 12 weeks, followed by remission after treatment
- a continuation phase of four to nine months, during which time relapses sometimes occur
- a maintenance phase of a year or more, with a potential for recurrence

Studies have revealed relapse rates between 7% and 26% (usually about 20%) with antidepressants, compared with rates of 19% to 56% (usually, 40%–50%) with placebo. Although most

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Meeting Highlights

157th Annual Meeting of the American Psychiatric Association: Psychotherapy and Psychopharmacology

Dissolving the Mind–Brain Barrier

Reuben B. David

More than 26,000 interested professionals attended the 157th annual meeting of the American Psychiatric Association in New York from May 1–6, 2004. Sessions were held at three different venues in the city. Topics included advances in drug research, mental health, personality disorders, suicide, aging, anxiety, and depression.
Meeting Highlights: American Psychiatric Association

Experts agree that the treatment of depression should continue for four to six months or up to a year after acute recovery, there have been few controlled data to define the treatment period. In one open-label study of fluoxetine (Prozac®, Eli Lilly) treatment for 14, 38, or 50 weeks, the rate of relapse at 14 weeks was significantly reduced (26%), compared with a rate of 49% for placebo. The rate of relapse after 38 weeks of treatment was 9%, compared with a rate of 23% for placebo. At 50 weeks, the reduction rates (11% for treated patients vs. 16% for placebo patients) were not significant, suggesting the need for at least six weeks of continuation therapy after a period of acute (short-term) treatment of roughly 12 weeks.

On the basis of these findings, the present study was designed to determine whether duloxetine HCl (DULX, Cymbalta®, Eli Lilly), at a starting dose of 60 mg once a day, would be effective in preventing relapse of depressive symptoms in patients who had previously responded to the drug. DULX is an inhibitor of both serotonin and norepinephrine uptake and has demonstrated efficacy in MDD in six short-term studies of (eight to nine weeks’ duration).

The present trial enrolled 553 patients. Patients received open-label DULX 60 mg once daily for 12 weeks. Thereafter, the responders (n = 278) were randomly selected to continue therapy for 26 weeks with either DULX or placebo in a double-blind study. The mean age of the responders was 45 years; two-thirds of the patients in the DULX group were women, and three-quarters of the patients in the placebo group were women. Patients experiencing relapse were entered into a “rescue” phase (12 weeks), with some (n = 29) assigned to receive a doubledose of DULX at 60 mg twice a day.

Participants met the DSM-IV criteria for MDD, as assessed by the modified Mini International Neuropsychiatric Interview (MINI) and the 17-item Hamilton Psychiatric Rating Scale for Depression (HAM-D17), for a total score of 18 or greater and a Clinical Global Impressions–Severity (CGI-S) score of 4 or more at visits 1 and 2.

Responders were defined by a HAM-D17 score of 9 or below, by a CGI-S score of 2 or less, and by no longer meeting the criteria for MDD at weeks 10 and 12. Relapse was defined by an increase in the CGI-S score of 2 points or more, as compared with the scores at week 12, for two consecutive visits in addition to meeting MINI depression module MDD criteria. Because the effects of DULX on both serotonin and norepinephrine have been known to be beneficial for pain, investigators assessed pain through a 100-point Visual Analogue Scale (VAS).

In the continuation phase, the HAM-D17 total scores increased significantly (P < .05) within a week of randomization for the placebo group and remained elevated through 38 weeks. A slight increase in HAM-D17 scores in the DULX group immediately after randomization might be attributed to the patients’ awareness of the possibility that they were not receiving active treatment. Relapse rates significantly favored DULX (17.4% of treated patients vs. 28.5% of placebo patients; P < .05) by protocol-defined criteria. When relapse was evaluated by investigators, the differences were more pronounced (21.9% vs. 43.1%; P < .001).

Among 56 patients in “rescue” treatment at 60 mg once daily, 77% responded (a 50% reduction or more in HAM-D17 scores) and 57% experienced remission (defined as a HAM-D17 score of 7 or below). Among 29 patients receiving 60 mg twice daily, 62% responded and 38% experienced remission.

Overall, DULX decreases were consistent for all HAM-D17 components and for seven of eight VAS components. Adverse drug events (ADEs) were similar to those found with other selective serotonin reuptake inhibitors (SSRIs), with the addition of some dry mouth, constipation, and sweating, consistent with the norepinephrine component of DULX. Similarly, an increase in the heart rate of approximately 1.5 beats per minute is attributable to norepinephrine reuptake inhibition.

The investigators concluded that DULX 60 mg once daily was effective in preventing relapse of MDD in patients who responded to short-term therapy. The safety and tolerability profile of DULX is similar to that of the most widely prescribed “modern” antidepressants. A “dose-doubling” strategy is effective, safe, and tolerable for most patients experiencing MDD relapse.

Five-Year Effects of Rivastigmine on Cognitive Performance

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Alzheimer’s disease (AD) is characterized by a relentless decline in cognitive performance and in the ability to perform normal daily tasks. Untreated or placebo-treated patients with AD show an average annual deterioration of about three points on the Mini-Mental State Examination (MMSE) or, depending on baseline levels, five to seven points on the Cognitive subscale of the Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-Cog). Short-term symptomatic treatments, such as cholinesterase inhibitors, are available for mild-to-moderate AD, but achieving further delay in cognitive decline or slowing long-term deterioration of symptoms would be clinically meaningful.

An earlier five-year study of rivastigmine (Exelon®, Novartis) suggested slowed deterioration when MMSE scores were compared with modeled projections. The ADAS-Cog, however, provides a more extensive and sensitive assessment of cognitive function than the MMSE. In addition, the Global Deterioration Scale (GDS) can be used to evaluate the clinical meaningfulness of ADAS-Cog.

Investigators pooled data from large, open-label extension studies of ADAS-Cog scores in 1,998 patients. In those studies, patients completing placebo-controlled rivastigmine trials had been invited to continue open-label rivastigmine (up to 12 mg) for up to five years. Mean ADAS-Cog scores and mean changes from baseline were calculated and compared with validated projections for untreated decline. They assessed the length of time that patients’ scores remained above predetermined ADAS-Cog levels.

During the evaluation period, 22.4% of the patients had withdrawn from the study because of ADEs, and 16% withdrew their consent for other reasons. The baseline characteristics of the remaining patients were similar to those of the entire group, but their cognitive impairment was milder; a mean ADAS-Cog score of 17.4 vs. 24.6 for the overall population and a mean GDS score of 3.7 vs. 4.1 for the overall population.

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The ADAS-Cog score threshold of 23 corresponded to moderate dementia (a GDS score of 4); a threshold of 33, moderately severe dementia (a GDS score of 5), and a threshold of 45, severe dementia (a GDS score of 6). For model-based untreated patients, mean ADAS-Cog scores increased beyond the threshold for moderately severe dementia (ADAS-Cog = 33) at approximately 1.5 years.

For patients receiving rivastigmine, the ADAS-Cog scores exceeded 33 after 2.5 years of treatment. Subsequently, mean ADAS-Cog scores increased past the severe AD threshold of 45 at approximately three years for the model-based untreated patients, compared with the rivastigmine-treated patients, who had not passed that threshold at five years (36.8 for the 75 patients remaining in the study).

The projected ADAS-Cog score for untreated patients was 56.9 at five years. The observed mean increase from baseline at five years in ADAS-Cog for the rivastigmine-treated patients was 19.4 points; for the untreated model-based patients, it was 27.3 points.

The most common side effects were gastrointestinal, and these tended to subside in a few weeks after the patients were stabilized on an acceptable dose.

In general, these results suggest that rivastigmine, which is a sustained dual inhibitor of acetylcholinesterase and butyrylcholinesterase, might have long-term clinical efficacy in AD patients. It appeared to slow the decline of cognitive symptoms by half. Approximately 28% of the cholesterol values in the RSP group became abnormal, and that figure was reduced by 5% with the addition of DVPX.

Mean doses of antipsychotic agents (days 6–28) were 15.0 mg/day for OLZ, 14.9 mg/day for DVPX + OLZ, 6.0 mg/day for RSP, and 6.0 mg/day for DVPX + RSP. The mean modal daily dose of DVPX (range, 500–3,500 mg/day) was 2,363 mg/day for DVPX + OLZ and 2,258 mg/day for DVPX + RSP. After four weeks, the total cholesterol increased from the baseline value by 26.62 mg/dl in the OLZ group, by 9.64 mg/dl in the RSP group, and by 0.87 mg/dl in the DVPX + OLZ group; it decreased by 13.44 mg/dl in the DVPX + RSP group.

The cholesterol levels of 56% of patients that had been in the normal range at baseline were shifted upward into the abnormal range after OLZ therapy. Adding DVPX cut this rate by about half. Approximately 28% of the cholesterol values in the RSP group became abnormal, and that figure was reduced by 5% with the addition of DVPX.

There were no correlations between baseline weight, body mass index, and total cholesterol changes. Increases in liver enzymes (serum alanine and aspartate transaminases, or AST and ALT) observed in the OLZ and RSP monotherapy groups were ameliorated with the addition of DVPX. There were no increases in the burden of side effects with the addition of DVPX, and there were fewer patient withdrawals from the study in the combination groups than in the monotherapy groups.

The investigators concluded that adding DVPX to OLZ or RSP therapy resulted in a decrease or in no change in total cholesterol levels. Further longer-term studies are under way.

Over the long-term, the 10% increase in total cholesterol observed at four weeks with OLZ represents a 20% to 30% increase in cardiovascular risk. The benefit of DVPX in preventing patients’ cholesterol values from being pushed up into the abnormal total range, combined with the improved antipsychotic efficacy of DVPX, is substantial. With combination treatment, it may be possible to reduce the typical length of a hospital stay for schizophrenic patients from 14 to seven days.

REFERENCES