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Late-Breaking Clinical Developments

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# New and Emerging Data in the Management of ADHD

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ADHD Poster Coverage of the 19th Annual U.S. Psychiatric &  
Mental Health Congress in New Orleans



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## TARGET AUDIENCE

This activity is designed for psychiatrists in general practice, psychiatrists specializing in pediatric and child/adolescent psychiatry, pediatricians, and primary care physicians.

## LEARNING OBJECTIVES

After completing this activity, participants should be able to:

- Describe the new understanding of the incidence and burden of childhood and adult attention-deficit/hyperactivity disorder (ADHD)
- Summarize newly presented data on the safety, efficacy, and tolerability of current and emerging pharmacotherapy for the management of ADHD
- Apply the latest data on the pharmacologic treatment options and the challenges presented by patient compliance to support the effective management of ADHD

Release Date: April 25, 2007, Expiration Date: April 25, 2008

There is no fee associated with this activity.

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**Dr. Andrews:** Speakers Bureau: Forest Laboratories, Wyeth Pharmaceuticals, sanofi-aventis U.S., Eli Lilly and Company, Pfizer, Sepracor

**Dr. Maypole:** Consultant—Shire Pharmaceuticals Inc.

Planning Committee Kay Weigand, University of Cincinnati; Randy Robbin and John Savage, Princeton CME; Kristin Dickie and Mary Johnson, Princeton Media Associates, have disclosed no relevant financial relationships with any commercial interests.

The University of Cincinnati and Princeton CME require faculty to inform participants whenever off-label/unapproved uses of drugs or devices are discussed in their presentation.

The following off-label/unapproved drugs or devices are discussed: guanfacine and SPD465 in the treatment of ADHD.

## GRANT SUPPORT

This activity is supported by an unrestricted educational grant from Shire Pharmaceuticals Inc.

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# New and Emerging Data in the Management of ADHD

Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by pervasive inattention and/or hyperactivity-impulsivity and results in significant functional impairment. The Centers for Disease Control and Prevention estimates that 4.4 million children and adolescents 4 to 17 years of age have been diagnosed with ADHD, and 2.5 million are currently receiving medication to treat this disorder.<sup>1</sup> Although often thought of as a childhood condition, ADHD frequently persists into adulthood: data from the National Comorbidity Survey Replication (NCSR), a community-based survey which tracks the prevalence of ADHD, indicate that an estimated 4.4% of US adults 18 to 44 years of age experience ADHD symptoms and degrees of associated disability.<sup>2</sup>

ADHD has important social and functional implications for children, adolescents, and adults. ADHD can cause a pattern of chronic impairment in multiple life domains—including work, school, and at home—significantly impacting the patient's quality of life. ADHD is also associated with a high prevalence of comorbidities, particularly other mental disorders and an increased risk of substance abuse.<sup>2</sup> The implications for adult functionality are particularly significant: compared to adults without ADHD, adults with ADHD experience greater deficits in self-care, mobility, and cognition; a higher number of missed workdays; and both productive and social role impairment.<sup>2</sup> Furthermore, adults with ADHD have been found to have higher rates of comorbid illness, as well as increased rates of problem drinking, lower educational attainment, and greater emotional and interpersonal difficulties.<sup>3</sup>

## ADHD Assessment Scales

**ADHD Rating Scale (ADHD-RS) and ADHD-RS Fourth Edition (ADHS-RS-IV):** Scale of 18 ADHD symptoms ranging in severity from 0 (none) to 3 (severe); decreasing scores over time indicate improvement in symptoms.

**ADHD Self-Report Scale (ADHD-SRS):** Measure of manifestations of ADHD symptoms in adults consistent with *DSM-IV* criteria; consists of 18 criteria rated by frequency of symptoms from never to very often.

**Clinical Global Impression (CGI) scales:** Measure of investigators' overall impression of improvement and severity of ADHD symptoms in a clinical setting; severity (CGI-S) is second of 2 subscales.

**Conners' Adult ADHD Rating Scale (CAARS):** Measure of a broad range of problem behaviors using 9 empirically derived scales. The measures include 3 *DSM-IV* symptom measures (Inattentive, Hyperactive-Impulsive, and Total ADHD symptoms), a 12-item ADHD Index, and an Inconsistency Index for identifying random or careless responding.

**Permanent Product Measure of Performance (PERMP):** Measure of age-adjusted math test scores determined by the number of problems attempted and number of correct answers over 10 minutes.

**Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scales:** Measure of classroom manifestations of ADHD assessment via 13 items. The ratings are based on the frequency and quality of behaviors, as observed by raters. Points are scored on subscales of attention (SKAMP-A) and deportment (SKAMP-D). A lower score at a single time point or a cumulative reduction over multiple time points indicates improved behavior.

ADHD = attention-deficit/hyperactivity disorder; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition*.

The consequent economic burden of ADHD is considerable. One literature review suggests that the annual cost of ADHD in children and adolescents ranges between \$12,005 and \$17,458 per patient; assuming a 5% prevalence rate, the cost to society is estimated to range between \$36 billion and \$52 billion annually.<sup>4</sup> A literature review by Matza et al found that adults with ADHD had substantially higher annual medical costs (\$4929-\$5651) than matched controls (\$1473-\$2771).<sup>5</sup> Additional costs associated with adult ADHD include expenses related to criminality, psychiatric and medical comorbidities, motor vehicle accidents, and work loss.<sup>5</sup>

Given the significant clinical and economic burden of ADHD, clinicians should carefully assess and treat patients with symptoms indicative of this diagnosis. Adequate treatment, however, remains challenging, given issues such as underdiagnosis, patient noncompliance with prescribed therapies, and questions regarding relative efficacy of treatment options. New research is providing information about the efficacy and safety of emerging and existing therapies, optimal dosing to attain treatment targets, and strategies to enhance patient compliance.

The posters presented at the 2006 U.S. Psychiatric & Mental Health Congress, held in New Orleans, Louisiana, on November 16, 2006, provide new information regarding ADHD prevalence; patient adherence to prescribed medical therapy; effectiveness of stimulant versus nonstimulant treatment; and the efficacy of investigational, recently approved, and existing ADHD therapies in children, adolescents, and adults. Summarized here are poster highlights, selected from the entirety of posters addressing the topic of ADHD, that were not previously reviewed in *First Report*®.

## ADHD May Be Underdiagnosed as a Comorbidity of Other Psychiatric Conditions<sup>6</sup>

Adults with a primary diagnosis of depression, bipolar disorder, or an anxiety disorder may also have comorbid ADHD that is undiagnosed and, therefore, untreated, according to a claims analysis performed by Adler et al.

NCSR data indicate that ADHD is a common comorbidity that appears in conjunction with other primary psychiatric diagnoses such as depression, bipolar disorder, and anxiety disorders. Adler et al performed a longitudinal retrospective claims analysis of medical and prescription databases to evaluate the rates of comorbid ADHD in patients with other psychiatric disorders and compared these rates with NCSR data to determine the extent of undiagnosed ADHD in patients with these conditions.

Researchers reviewed 12 months of claims involving patients 18 years of age and older with a new *International Classification of Diseases Ninth Revision* coded diagnosis of ADHD, depression (major depressive disorder and dysthymia), bipolar disorder, or an anxiety disorder. The study identified adult patients with a new diagnosis of one of the targeted disorders examined and found total new diagnoses in the 12-month study period were: ADHD—900,897; bipolar disorder—1,148,175; anxiety disorder—6,573,576; and depression—12,036,905.

The claims analysis revealed a comorbid ADHD diagnosis in 2.5% of patients with bipolar disorder and in 1.7% of patients with either depression or an anxiety disorder. In contrast, NCSR data indicate that ADHD is a comorbid diagnosis in 32% of adult patients with depression, 21.2% of patients with bipolar disorder, and 9.5% of patients with an anxiety disorder.

Researchers concluded that physicians should screen for ADHD in adult patients presenting with common psychiatric disorders, given the significant underdiagnosis of comorbid ADHD indicated by the discrepancy in claims data compared with NCSR statistics.

## Research Suggests Poor Adherence to ADHD Medication Based on Prescription Fill Rates<sup>7</sup>

A study by Hodgkins et al indicates that, based on prescription fill rates, compliance rates with pharmacologic ADHD therapy are low. Over 12 months, 80.7% of study participants filled 3 or less prescriptions for ADHD medications of all types. Researchers observed a direct relationship between the number of office visits and the number of prescriptions filled for the initially prescribed ADHD medication, suggesting that more frequent office follow-up may improve compliance.

The 12-month, longitudinal, retrospective analysis of medical and prescription databases evaluated the relationship between the number of annual office visits with the treating physicians and prescription fill rates for common ADHD medical therapies. Patients included in the analysis were required to be 6 years of age and older, newly diagnosed with

ADHD, and initiating treatment with a prescription for a 30-day supply of a Food and Drug Administration (FDA)-approved medication for ADHD management. Statistical analysis of the data was performed using a 2-sided Pearson correlation coefficient to describe the relationship between the number of office visits and the number of prescriptions filled over the 12-month period; the level of significance was set at  $P < .05$ .

Claims data from 16,383 patients meeting all inclusion criteria indicated that, over 12 months (from January 1, 2005, to December 31, 2005), patients had a mean of 2.7 office visits and filled an average of 4.8 prescriptions. The analysis revealed poor compliance with medical therapy: 78.2% of patients had 1 to 3 office visits and 53.3% filled 1 to 3 prescriptions; 41.2% of patients tracked had only 1 office visit, and 27.4% filled only 1 prescription. A strong positive correlation was found between the number of office visits and the number of prescriptions filled (Table); patients with 7 or more office visits exhibited increased medication adherence (>50%), with 6 or more prescriptions filled over 12 months.

The study investigators determined that the data presented a direct relationship between the number of office visits and the number of prescriptions filled, suggesting a positive link between office follow-up and compliance. This conclusion led the study investigators to suggest that more frequent office follow-up may lead to improved medication adherence among patients with ADHD.

**Table. Summary of Medication Adherence Ratios, by Number of Office Visits<sup>7</sup>**

Number of Office Visits	Mean Number of Prescriptions per Visit	Medication Adherence Ratio (%) <sup>*</sup>
1-2	4.1-4.6	34-38
3-6	5.3-5.9	44-49
7-10	6.0-6.4	50-53
11	8.4	70
12+	7.4	62

\*The medication adherence ratio (%) was defined as the mean number of prescriptions filled divided by the total number of possible refills over 12 months (12) x 100.

## Prescription Fill Rates Higher with Long-Acting Versus Short-Acting Medications<sup>8</sup>

Adherence to ADHD medication therapy was found to be generally poor, but comparatively better with long-acting versus short-acting medications in a 12-month, longitudinal, retrospective claims analysis by Hodgkins et al.

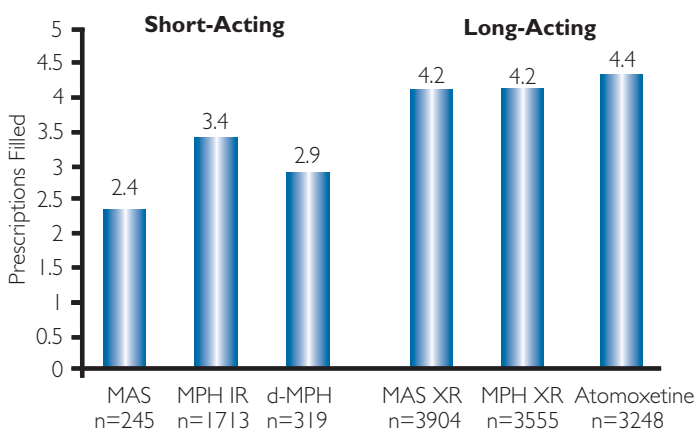
The study tracked the number of ADHD prescriptions filled by patients for the initially prescribed medication for 12 months following the index date and compared fill rates between long-acting and short-acting medications. A total of 12,984 patients met the following inclusion criteria: patients 6 years of age and older, newly diagnosed with ADHD, and initiating treatment with a prescription for a 30-day supply of

the stimulants mixed amphetamine salts (MAS), MAS extended release (MAS XR), methylphenidate immediate release, methylphenidate extended release, dexamethylphenidate, or the long-acting nonstimulant atomoxetine. The number of patients receiving a new prescription of each medication studied were: MAS—245; MAS XR—3904; methylphenidate—1713; methylphenidate extended release—3555; dexamethylphenidate—319; and atomoxetine—3248.

The study revealed that medication compliance was poor, regardless of medication type, with most patients filling 3 or less prescriptions over the 12-month study period. However, analysis by medication type revealed that long-acting medication prescriptions were filled with greater frequency than short-acting medication prescriptions. The mean number of short-acting prescriptions filled per patient over 12 months was 2.9, 32% lower than the mean number of long-acting prescriptions filled per patient (4.3). The mean number of prescriptions filled, identified by medication type, is shown in the [Figure](#).

Researchers concluded that medication adherence may be improved with use of long-acting medications as well as more frequent follow-up with patients to determine and encourage compliance.

**Figure. Mean Number of Prescriptions Filled Per Patient over 12 Months\*\***



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\*Data shown are the mean number of prescriptions filled for short-acting or long-acting medications per patient from the index date over 12 months.

MAS = mixed amphetamine salts; MPH IR = methylphenidate immediate release, d-MPH = dexamethylphenidate; XR = extended release.

### Meta-Analysis Suggests Greater Efficacy of Stimulant over Nonstimulant Therapy for ADHD<sup>9</sup>

A meta-analysis, performed by Faraone et al to assess the influence of medication type and study design features on the effects of the medication on ADHD symptoms, indicates that psychostimulant therapy tends to be more effective than nonstimulant therapy for ADHD symptom management in children.

Study investigators conducted a literature search to identify

randomized, double-blind, placebo-controlled treatment studies of children 8 to 15 years of age with ADHD diagnosed using *Diagnostic and Statistical Manual of Mental Disorders (DSM), Revised Third Edition* or *DSM-Fourth Edition (DSM-IV)* criteria. To be included, studies had to be conducted after 1979, follow subjects for at least 2 weeks, and present the means and standard deviations of either change or end point scores for the drug and placebo groups. Data derived from the highest dose were used when studies presented data on more than 1 fixed dose. Studies were excluded if behavior was rated in laboratory environments, fewer than 20 subjects were included in either the drug or placebo groups, or only ADHD sample populations diagnosed with a comorbid condition were included.

Twenty-nine published trials involving 4464 subjects and evaluating 15 ADHD medications were included in the analysis. The trials, which employed 17 different outcome measures, were stratified into 3 categories based on the drugs studied: nonstimulant/other, short-acting stimulant, and long-acting stimulant. Data extracted from each study included year of publication; name of dependent outcome measure; name of drug; distribution of *DSM-IV* subtypes in the study sample; study design (parallel vs crossover); outcome score used (change score vs posttreatment score); type of rater (parent, teacher, clinician, self); mean age of study population; percentage of male subjects; dosing method (fixed dose vs titration to best dose); use of placebo lead-in; and exclusion of nonresponders. Effect sizes for dependent measures in each study were determined by subtracting the mean of the placebo group from the mean of the active drug group, and then dividing by the pooled standard deviation of the groups. In studies where results were reported as a score change from baseline, effect size was defined as the difference between change scores; effect sizes for studies reporting end point scores were defined as the difference between end point scores.

After correcting for study design variables, the analysis indicated that the average effect sizes of 0.90 for the short-acting stimulants and 0.83 for long-acting stimulants were significantly greater than the effect size of 0.62 for nonstimulants/other medications ( $P=.004$  with long-acting stimulants,  $P=.002$  with short-acting). Short- and long-acting stimulants did not differ greatly from one another in terms of effect size based on total ADHD scores in this analysis.

Studies of short- or long-acting stimulants more often used parallel groups rather than crossover designs and change from end point scores in place of baseline outcome scores compared with studies of nonstimulants or other medications.

The study investigators determined that, based on the meta-analysis data, stimulant therapy tends to be more effective than nonstimulant therapy in the management of ADHD symptoms in children and adolescents. Researchers caution against comparing specific medication effect sizes from different studies without accounting for variability in study design, as there was no uniformity across studies in how medication effectiveness was assessed.

## Phase 2 Trial Suggests Symptom Improvement with Recently-Approved Stimulant Treatment Comparable to MAS XR in School-Aged Children<sup>10</sup>

A 6-week treatment trial suggests that the recently FDA-approved stimulant lisdexamfetamine dimesylate (LDX) has efficacy comparable to MAS XR in controlling symptoms and behaviors in school-aged children with ADHD, as measured by SKAMP and PERMP scales in an analog classroom environment.

The phase 2, multicenter, randomized, double-blind, 3-treatment, 3-period crossover study by Biederman et al evaluated the efficacy and safety of 3 doses of LDX (30, 50, and 70 mg/day) and 3 doses of MAS XR (10, 20, and 30 mg/day) compared with placebo in 52 children 6 to 12 years of age with ADHD. Participants were required to have a primary diagnosis of ADHD combined or predominantly hyperactive-impulsive subtypes as defined by *DSM-IV-Text Revision* criteria.

After a 1-week screening and a 3-week titration period to optimal MAS XR dose, subjects were randomized among 3 cohorts and were treated with optimal dose MAS XR, LDX dose comparable to optimal MAS XR dose, and placebo as follows:

- Cohort A: 1 week each of MAS XR 10 mg per day, LDX 30 mg per day, and placebo
- Cohort B: 1 week each of MAS XR 20 mg per day, LDX 50 mg per day, and placebo
- Cohort C: 1 week each of MAS XR 30 mg per day, LDX 70 mg per day, and placebo

Each week, the study medication was administered at home on days 1 through 6 and in the analog classroom on day 7. Each classroom day lasted 13 hours, with 30-minute classroom sessions scheduled at approximately 1, 2, 3, 4.5, 6, 8, 10, and 12 hours following the study dose. The primary efficacy outcome measure of least squares (LS) mean of the average score from the SKAMP-Department Rating Scale and the secondary efficacy outcome measures of SKAMP-Attention, PERMP-attempted, and PERMP-correct were collected during each session. Of 52 subjects, 50 (96%) completed the trial; the 2 that discontinued did so during the placebo period of the study.

LDX exhibited efficacy and an adverse event profile comparable to MAS XR in the study population. Both active treatments were superior to placebo in controlling ADHD symptoms and behaviors, and no significant differences between the 2 medications were exhibited in any of the cohorts. The LS mean SKAMP-Department score was 0.8 for LDX and MAS XR, compared with 1.7 for placebo ( $P<.001$ ); SKAMP-Department scores for each optimal dose cohort indicated positive treatment effects for all doses of both active treatments as follows:

- Cohort A: 0.7 for LDX 30 mg and 0.6 for MAS XR 10 mg, compared with 1.1 for placebo ( $P<.05$ )
- Cohort B: 0.7 for LDX 50 mg and 0.9 for MAS XR 20 mg, compared to 1.7 for placebo ( $P<.0001$ )
- Cohort C: 0.8 for LDX 70 mg and 0.9 for MAS XR 30 mg, compared to 1.8 for placebo ( $P<.0001$ )

The secondary efficacy outcome measures reflected similar favorable results. The LS mean SKAMP-Attention score for both LDX and MAS XR was 1.2, compared with 1.8 for placebo ( $P<.0001$ ). The LS mean PERMP-attempted scores were 133.3 and 133.6 for LDX and MAS XR, respectively, compared with 88.2 for placebo ( $P<.0001$ ), while the LS mean PERMP-correct scores were 129.6 and 129.4 for LDX and MAS XR, respectively, compared with 84.1 for placebo ( $P<.0001$ ).

Treatment-emergent adverse events were documented throughout the study. Vital signs were collected at all visits, laboratory parameters and physical examination at screening and final visit, and electrocardiogram (ECG) measurements at screening, visits 5 through 8, and final visit. Serious adverse events were also recorded at 30-day telephone follow-up. The most common adverse events occurring during dose titration of MAS XR were headache (15%), decreased appetite (14%), and insomnia (10%); 63% and 37% of adverse events were mild or moderate, respectively, and no adverse events were reported as severe. Adverse events reported during double-blind treatment with LDX were insomnia (4 patients), decreased appetite (3), and anorexia (2); with MAS XR, upper abdominal pain (2), decreased appetite (2), vomiting (1), and insomnia (1); and with placebo, vomiting (2), upper abdominal pain (1), and insomnia (1). Both diastolic blood pressure and pulse were slightly higher in treated patients compared with individuals receiving placebo, with 5-mm Hg and 3-mm Hg increases in blood pressure and 7-beats-per-minute and 5-beats-per-minute increases in pulse with LDX and MAS XR, respectively. No serious adverse events were reported during the double-blind period of the study, with 62% of reported adverse events being mild in severity, and 38% considered moderate; no clinically significant ECG findings were reported in either active treatment arm of the study.

Researchers concluded that in school-aged children, LDX has comparable efficacy and a similar adverse effect profile with MAS XR. Additionally, the documented changes in blood pressure and pulse with both treatments were noted as small, with no trends being revealed.

## Long-Acting Investigational Stimulant Improves Adult ADHD Symptoms for Up to 16 Hours at Low Dose<sup>11</sup>

SPD465, a triple-bead, mixed salt of a single-entity amphetamine, provides a full day of symptom control in adults with ADHD as measured by PERMP, ADHD-SRS, and ADHD-RS scores, according to data from a 1-week treatment study. SPD465 was shown to provide up to 16 hours of symptom control in the study population, compared with the 10 to 12 hours of symptom control generally provided by current long-acting stimulants used in adult ADHD treatment.

SPD465 contains 3 types of beads enabling immediate, delayed, and sustained release of the agent; this formulation is designed to achieve prolonged ADHD symptom control with a single morning dose.

Conducted by Wigal et al, the phase 2, randomized, double-

blind, multicenter, 2-period, 2-treatment, crossover study evaluated the safety and efficacy of SPD465 compared with placebo in adults 18 to 55 years of age with ADHD. Of 79 subjects, 73 (92%) completed the study; 2 subjects withdrew due to possible treatment-related adverse events while on SPD465 25 mg.

After screening, subjects were randomized to receive 25 mg of SPD465 or placebo; subjects taking psychostimulant medication underwent a washout period of at least 7 days prior to baseline assessment. Subjects took a single morning dose of the assigned treatment during each 7-day study period. On day 7, behavioral assessments were conducted in a controlled adult workplace laboratory at 0.5 hours pre-dose and at 2, 4, 8, 12, 14, and 16 hours post-dose. The primary efficacy measure was the PERMP total score; secondary measures to compare the duration of effect between SPD465 and placebo included the PERMP-attempted and PERMP-correct, the ADHD-SRS, and the ADHD-RS. Safety and tolerability assessments, which included treatment-emergent adverse events, vital signs, laboratory findings, ECG data, and sleep quality, were also conducted during the 7-day treatment period, and telephone follow-up was conducted approximately 30 days after the final study dose to identify ongoing or new adverse events.

Results indicated greater efficacy with SPD465 compared with placebo; SPD465 resulted in higher mean PERMP total scores on day 7 beginning at 4 hours post-dose and persisting through 16 hours post-dose. Furthermore, at all time points measured, mean numbers of math problems attempted and answered correctly were higher with SPD465. Superior efficacy of SPD465 over placebo at all time points measured was also indicated by total scores on the ADHD-SRS ( $P < .0001$  at 5.5, 11, and 16.5 hours) and ADHD-RS ( $P < .05$  from 11 to 16.5 hours).

No serious adverse events were reported during the study. The most common adverse events for SPD465 noted during the trial included decreased appetite (22.4%), insomnia (25%), and dry mouth (14.5%). Mean hematology and clinical chemistry values exhibited little change from screening to treatment, and changes in mean pulse, blood pressure, and ECG values were not clinically significant.

Study investigators noted that based on the week-long trial data, SPD465 may be useful for maintaining symptom improvement during waking hours without the need for repeat dosing.

### 50- and 75-mg Doses of Investigational Stimulant Shown to Have 16-Hour Duration of Effect in Adults with ADHD<sup>12</sup>

A 1-week treatment trial conducted by Wigal et al found that a single morning dose of SPD465 at doses of 50 and 75 mg significantly improved symptoms of adult ADHD for up to 16 hours compared with placebo ( $P < .0001$ ). The researchers assessed the duration of effect and safety of SPD465, a triple-bead, mixed salt of a single-entity amphetamine, at doses of 50 mg and 75 mg and an immediate-release formulation of MAS (MAS IR) compared with placebo.

The phase 2, randomized, double-blind, multicenter, 3-period, 3-treatment, crossover study was conducted in adult subjects 18 to 55 years of age with ADHD. Of 86 subjects, 77 (90%) completed the study. Seven patients were lost due to treatment-related adverse events; 6 during SPD465 treatment and 1 during placebo treatment.

After screening, subjects were randomized to receive either 50 or 75 mg of SPD465, MAS IR, or placebo; subjects taking psychostimulant medication underwent at least a 7-day washout period prior to baseline assessment. Subjects took a single morning dose of the assigned treatment each morning during each of the 7-day study periods. Both SPD465 treatment doses were titrated so that subjects reached the assigned dose by day 4. On day 7, assessments were conducted in a controlled environment at 0.5 hours pre-dose and at 2, 4, 8, 12, 14, and 16 hours post-dose. The primary efficacy measure was the PERMP total score; secondary measures comparing duration of effect included the PERMP-attempted and PERMP-correct, ADHD-SRS, and ADHD-RS. Safety and tolerability assessments were conducted on days 4 and 7, and telephone follow-up was conducted approximately 30 days after the final study dose to identify ongoing or new adverse events.

Results indicated greater efficacy of SPD465 compared with placebo. Mean PERMP total scores on day 7 were significantly greater with SPD465 50 mg/75 mg compared with placebo at all post-dose assessment points ( $P < .0001$ ). Furthermore, at all assessment points, mean numbers of math problems attempted

**Table. Most Common Treatment-Related Adverse Events (%)<sup>12</sup>**

SPD465 50 mg (n=42)	
Insomnia	(26.2)
Anorexia	(14.3)
Decreased Appetite	(11.9)
Headache	(9.5)
Dry Mouth	(9.5)
SPD465 75 mg (n=43)	
Insomnia	(44.2)
Dry Mouth	(27.9)
Anorexia	(27.9)
Decreased Appetite	(25.6)
Headache	(25.6)
MAS IR 25 mg (n=79)	
Insomnia	(16.5)
Anorexia	(13.9)
Headache	(13.9)
Dry Mouth	(10.1)
Decreased Appetite	(8.9)
Placebo (n=81)	
Headache	(4.9)
Insomnia	(3.7)
Decreased Appetite	(2.5)
Anxiety	(2.5)
Nausea	(2.5)

MAS IR = mixed amphetamine salts immediate release.

and answered correctly were higher with SPD465 50 mg/75 mg compared with placebo. On the ADHD-SRS measure, SPD465 was superior to placebo at all time points, but was first shown to be significantly superior to placebo at 5.5 hours post-dose ( $P<.0001$ ), at which time MAS IR was also superior to placebo ( $P<.0001$ ). Only SPD465 was superior to placebo at 16.5 hours post-dose. On the ADHD-RS measure, both SPD465 and MAS IR were first shown to be significantly superior to placebo during the cycle 5.5 hours to 11 hours post-dose ( $P<.0001$ ), and SPD465 remained significantly superior to placebo during the period ending at 16.5 hours post-dose ( $P=.01$ ).

Adverse events observed with SPD465 were consistent with those associated with amphetamines. The most common adverse events considered related to the study medications are described in the [Table](#). Study investigators noted that the higher adverse event incidence associated with the 75-mg dose of SPD465 may be partly attributable to the rapid (4-day) titration schedule used in the study. Small mean changes in ECG parameters were noted, but were not considered clinically significant. Sleep quality was largely unchanged in subjects on placebo, MAS IR, and SPD465 50 mg, but decreased with SPD465 75 mg, and sleep duration increased slightly with both doses of SPD465.

According to researchers, the study data suggest that SPD465 may exert symptom control into the late evening hours following a single morning dose.

## Investigational Stimulant Medication Improves Adolescent ADHD Symptoms for Up to 16 Hours<sup>13</sup>

A 3-week treatment trial conducted by Wigal et al assessed the duration of effect and safety of SPD465, a triple-bead, mixed salt of a single-entity amphetamine, at doses of 25 and 50 mg and MAS IR compared with placebo in adolescents with ADHD. The researchers found that a single morning dose of SPD465 25 mg and 50 mg significantly improved symptoms of subjects for up to 16 hours compared with placebo ( $P<.0001$ ).

The phase 2, randomized, double-blind, multicenter, 3-period, 3-treatment, crossover study was conducted in a laboratory school environment in adolescents 13 to 17 years of age with diagnosed ADHD based on *DSM-IV* criteria. Subjects were otherwise healthy and had a baseline ADHD-RS-IV score of 24 or greater. Of 84 subjects, 83 (99%) completed the study; 1 subject was lost to follow-up and never received MAS IR.

Subjects were randomized to receive either 25 mg or 50 mg of SPD465, 12.5 mg of MAS IR, or placebo during three 1-week intervals; subjects taking psychostimulant medication underwent at least a 7-day washout period prior to baseline assessment. Subjects took a single morning dose each day of the assigned treatment during each 7-day study period. Subjects on SPD465 50 mg were initiated at 25 mg and titrated to 50 mg at day 4. On day 7, assessments were conducted in a laboratory school environment at 0.5 hours pre-dose and at 2, 4, 8, 12, 14, and 16 hours post-dose. The primary efficacy measure was the PERMP total score; secondary measures comparing duration of effect included the PERMP-attempted and PERMP-correct, ADHD-SRS, and ADHD-RS. Safety and tolerability assessments

were conducted on day 4 or 5 of each treatment period, and telephone follow-up was conducted approximately 30 days after the final study dose to identify ongoing or new adverse events.

Results indicated greater efficacy with SPD465 compared with placebo. Mean PERMP total scores on day 7 were significantly greater with SPD465 25 mg/50 mg compared with placebo from 2 hours post-dose through 16 hours post-dose ( $P<.001$ ), and scores were significantly greater with SPD465 25 mg/50 mg compared with MAS IR at 16 hours post-dose ( $P=.003$ ). Furthermore, at all assessment points, mean numbers of math problems attempted and answered correctly were higher with SPD465 25 mg/50 mg compared with placebo.

No subjects discontinued the study prematurely due to an adverse event; adverse events observed with SPD465 were mild, and the types of adverse events experienced were consistent with those associated with amphetamines ([Table](#)). Sleep quality decreased slightly with SPD465 50 mg, but was largely unchanged in subjects on placebo, MAS IR, and SPD465 25 mg.

Researchers noted that a single morning dose of SPD465 enabled full-day coverage of ADHD symptoms in adolescents. Additionally, they indicated that the higher adverse event incidence associated with the 50-mg dose of SPD465 may be partly attributable to the rapid titration schedule used in the study.

**Table. Treatment-Related Adverse Events in Adolescents Most Commonly Associated with SPD465<sup>13</sup>**

Adverse Event	SPD465 25 mg (n=41)	SPD465 50 mg (n=43)	MAS IR 12.5 mg (n=83)	Placebo (n=84)
Any TEAE	18 (41.9)	32 (78.0)	14 (16.9)	15 (17.9)
Insomnia	9 (20.9)	23 (56.1)	2 (2.4)	0 (0.0)
Anorexia	4 (9.3)	11 (26.8)	1 (1.2)	1 (1.2)
Irritability	4 (9.3)	0 (0.0)	2 (2.4)	0 (0.0)
Decreased Appetite	1 (2.3)	7 (17.1)	1 (1.2)	2 (2.4)
Headache	1 (2.3)	6 (14.6)	2 (2.4)	5 (6.0)
Upper Abdominal Pain	1 (2.3)	4 (9.8)	1 (1.2)	0 (0.0)

MAS IR = mixed amphetamine salts immediate release; TEAE = treatment-emergent adverse event.

## Investigational Extended-Release Formulation of Off-Label Nonstimulant Allows for Once-Daily Dosing in Adult ADHD Treatment<sup>14</sup>

A minimization of plasma level fluctuations and a reduced pH dependency for medication release were shown to provide for 24-hour coverage of the investigational extended-release formulation of guanfacine in a review of 2 separate phase 1 studies.

Guanfacine immediate release (GIR), a nonstimulant alpha-2A adrenoceptor agonist approved as an antihypertensive agent, has been used off-label to treat ADHD in adults. A new formu-

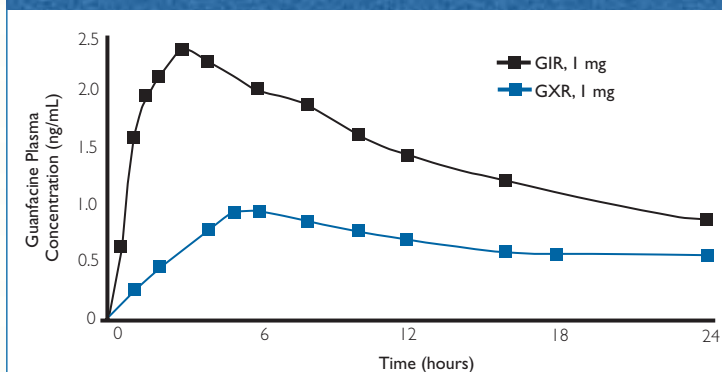
lation, guanfacine extended release (GXR), has been developed as a once-daily treatment for adult ADHD.

GXR was manufactured using a waterless process that involved blending and then compressing a dry powder. United States Pharmacopeia Apparatus II was used to perform in vitro dissolution testing over a 24-hour period. A validated high-performance liquid chromatography assay method specific for guanfacine was used to test samples.

Shojaei et al generated pharmacokinetic data on GXR from 2 separate phase 1, single-dose, crossover, open-label clinical studies in healthy adults. In one study, 12 subjects were randomized to receive oral GIR (1 mg) or GXR (1 mg) after fasting in a crossover design. Blood samples were collected at specific times over 72 hours for guanfacine measurement, with a 7-day washout between periods. In the second study, subjects were randomized to receive GXR 2 mg or 4 mg, manufactured at 1 of 2 facilities, after an overnight fast in a crossover design over 5 periods. Blood samples were collected at specific times over 96 hours for guanfacine measurement, with a 7-day washout between periods.

The in vitro dissolution profile of GXR indicated a reduced pH dependency for medication release and allowed for extended release of the medication for up to 24 hours. Profiles of plasma concentration over time showed that, in contrast to GIR, GXR prolonged the absorption phase, and provided slow, sustained increases in plasma concentration (Figure). Researchers concluded that the pharmacokinetics of GXR allow for once-daily dosing, potentially increasing patient compliance and reducing adverse events associated with plasma level fluctuations.

**Figure. Plasma Concentration Versus Time Curve<sup>14</sup>**



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GIR = guanfacine immediate release; GXR = guanfacine extended release.

### Nonstimulant ADHD Treatment Found Effective in Children and Adolescents with ADHD and Comorbid Anxiety<sup>15</sup>

Atomoxetine, a potent inhibitor of the presynaptic norepinephrine transporter, has been proven effective for treating ADHD in children and adolescents in previous trials. A 12-week trial by Sumner et al suggests that the drug is also effective

in children and adolescents with ADHD and comorbid anxiety.

The randomized, double-blind, placebo-controlled, multicenter trial was conducted in subjects 8 to 17 years of age who met DSM-IV criteria for both ADHD and anxiety disorder (generalized anxiety, separation anxiety, or social phobia) and had an ADHD symptom severity score of 1.5 or more standard deviations above age and gender norms assessed by ADHD-RS-IV Parent Version. Subjects were randomized to approximately 12 weeks of treatment with either atomoxetine or placebo. The target atomoxetine dose of 1.2 mg/kg per day could be increased to 1.8 mg/kg per day for inadequate responders, and all doses were split and administered twice daily. After 2 screening/assessment visits (2 weeks), patients underwent double-blind treatment with atomoxetine or placebo for visits 3 through 9 (9-18 days), open-label atomoxetine treatment for visits 9 through 13 (60 days), and atomoxetine treatment for an extension phase including visits 13 to 16 (30-90 days).

Primary efficacy measures included the ADHD-RS and the Pediatric Anxiety Rating Scale (PARS); the secondary efficacy measure was the Multidimensional Anxiety Scale for Children (MASC). Researchers found that atomoxetine demonstrated a large effect size (1.0) in ADHD according to the ADHD-RS, with a mean change from baseline of -10.5, compared to -1.4 on placebo ( $P < .001$ ). Atomoxetine had a moderate effect size (0.5) in anxiety according to the PARS, with a mean change from baseline of -5.5, compared with -3.2 on placebo ( $P = .011$ ). Furthermore, patients reported improvements in anxiety that were consistent with investigator ratings according to the MASC.

Of 87 patients receiving atomoxetine and 89 patients receiving placebo, 76% and 74%, respectively, completed the study, with the largest number—10 with atomoxetine and 13 with placebo—lost due to lack of efficacy. Only 2 patients on atomoxetine discontinued treatment due to an adverse event. The most common adverse events in the atomoxetine group were decreased appetite (11 patients), headache (11), upper abdominal pain (9), and vomiting (8); the most common adverse events with placebo were headache (7), nasopharyngitis (5), and cough (5).

Researchers concluded that atomoxetine was effective in the treatment of both ADHD and comorbid anxiety, with positive results reported in all patients as well as in eligible patients, who did not respond during placebo lead-in.

### FDA-Approved Nonstimulant Found Effective in Both Young and Older Adults in the Treatment of ADHD<sup>16</sup>

Atomoxetine, the only nonstimulant approved for ADHD treatment in children, adolescents, and adults, may be effective in treating ADHD in both young and older adults, although the benefit in younger adults appears to be greater, according to a post-hoc analysis of randomized controlled trial data.

Patients included adults with ADHD 18 years of age and older who were enrolled in 2 multicenter, randomized, placebo-controlled, double-blind trials of atomoxetine. In each trial, atomox-

oxetine was initiated at a dose of 60 mg, evenly divided between a morning and a late afternoon/evening dose, for approximately 10 weeks. The dosage was increased to 90 mg per day after 2 weeks and 120 mg per day after 4 weeks for patients with continued symptoms. The primary outcome measure used in these 2 original trials was a comparison of atomoxetine and placebo using repeated measures mixed model analysis of post-baseline values of the CAARS.

The post-hoc analysis, conducted by Durell et al, compared mean changes from baseline on the CAARS Total ADHD Symptom Score and the CGI-S of younger adults (18-25 years of age) versus older adults (26-77 years of age). Researchers found that atomoxetine proved effective in both younger and older adults. The change from baseline to end point in the CAARS Total ADHD Symptom Score was -11.77 for atomoxetine compared with -8.38 on placebo in young adults ( $P=.041$ ) and -12.22 for atomoxetine compared with -8.36 on placebo in older adults ( $P<.001$ ). The change from baseline to end point in the CGI-S was -0.88 for atomoxetine compared with -0.52 on placebo in young adults ( $P=.006$ ) and -0.95 for atomoxetine compared with -0.55 on placebo in older adults ( $P<.001$ ). Both age groups took less time to respond to atomoxetine treatment compared with placebo. The younger adults had smaller variability on these outcome measures, although this may have been affected by the relatively small sample size of 29 placebo-treated and 26 atomoxetine-treated patients in the 18- to 25-year-old cohort.

Response rates for young adults were higher, with 56.4% experiencing a 25% or greater reduction on the CAARS Total ADHD Symptom Score, compared with 47.8% of older adults ( $P=.188$ ). Both age groups experienced similar tolerability effects, although older adults reported a greater number of sexual adverse events. The most common treatment-related adverse events for both groups are listed in the [Table](#).

Researchers noted that it took significantly less time for patients

**Table. TEAEs, by Age Group<sup>16</sup>**

18- to 25-Year-Olds			
Events, n (%)	Atomoxetine (n=26)	Placebo (n=29)	P Value
Headache	5 (19.2)	5 (17.2)	1.00
Insomnia	5 (19.2)	2 (6.9)	.236
Nasopharyngitis	4 (15.4)	4 (13.8)	1.00
Dry Mouth	3 (11.5)	2 (6.9)	.659
Nausea	3 (11.5)	3 (10.3)	1.00
Pharyngitis	3 (11.5)	2 (6.9)	.659
Decreased Appetite	3 (11.5)	0 (0.0)	.099
Constipation	3 (11.5)	0 (0.0)	.099
Sinusitis	3 (11.5)	2 (6.9)	.659
>25-Year-Olds			
Events, n (%)	Atomoxetine (n=237)	Placebo (n=244)	P Value
Dry Mouth	53 (21.7)	15 (6.3)	<.001
Headache	42 (17.2)	40 (16.9)	1.00
Nausea	29 (11.9)	10 (4.2)	.002
Insomnia	28 (11.5)	15 (6.3)	.055
Decreased Appetite	25 (10.2)	8 (3.4)	.003
Constipation	23 (9.4)	10 (4.2)	.030
Upper Respiratory Tract Infection	18 (7.4)	20 (8.4)	.736
Erectile Dysfunction	17 (10.9)	2 (1.3)	<.001
Decreased Libido	16 (6.6)	4 (1.7)	.010

TEAE = treatment-emergent adverse event.

in both age groups to respond to atomoxetine treatment compared with placebo, leading them to conclude that atomoxetine is an efficacious treatment choice for ADHD both in younger and older adults.

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