## Stroke History Raises Risk of Vascular Dementia

## BY KERRI WACHTER Senior Writer

PORTO, PORTUGAL — Stroke was associated with a nearly 20-fold increase in risk for vascular dementia in a univariate, retrospective, case-control analysis presented at the Fourth International Congress on Vascular Dementia.

Among 205 people with vascular dementia and their control cases, those with a history of stroke were 19 times more likely to develop vascular dementia in the univariate analysis, said Dr. Casey R. Caldwell, an internal medicine physician at the Mayo Clinic, Rochester, Minn. The association of dementia with stroke was stronger in men, who had an odds ratio of 28, than in women, who had an odds ratio of 16.

For the analysis, all Mayo Clinic health records from residents of Olmsted County, Minnesota, during the period 1994-2002 were screened for any of 40 diagnoses suggestive of dementia. This screening identified 1,736 potential subjects, among whom 205 cases of vascular dementia were identified using criteria from the National Institute of Neurological Disorders and Stroke and from the Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN).

The subjects were age- and gendermatched with community controls. Individuals were excluded as possible community control subjects if they had been diagnosed with dementia of any kind.

References: 1. Faraone SV, Biederman J. A controlled study of functional impairments in 500 ADHD adults. Presented at: 157th Annual Meeting of the American Psychiatric Association; May 5, 2004; New York, NY. 2. Data on file, Shire US Inc, 2006. 3. ADDERALL XR<sup>®</sup> [package insert]. Shire US Inc; Wayne, Pa: 2006. 4. Claxton AJ, Cramer J, Pierce C. A systematic review of the association between dose regimens and medication compliance. *Clin Ther*. 2001;23:1296-1310.

BRIEF SUMMARY: Consult the full prescribing information for complete product information. ADDERALL XR® CAPSULES CII Rx Only AMPLETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. PARTICULAR ATTENTION, SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY. MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS. NDICATIONS ATIONS RALL XR= is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). ficacy of ADDERALL XR= in the treatment of ADHD was established on the basis of two controlled trials in cf 12, one controlled trial in adolescents aged 13 to 17, and one controlled trial in adults who met DSM-IV= , along with extrapolation from the known efficacy of ADDERALL=, the immediate-release formulation of this <u>expression</u> verse event orexia (loss of appetite) CONTRAINDICATIONS Advanced arteriosclars ICATIONS teriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known ity or idiosyncrasy to the sympathomimetic amines, glaucoma. 0.7 lacebo-controlled 4-week study in adolescents with nt due to adverse events among ADDERALL XR≈-tre ue to insomnia and one patient each for depression Inued treatment due to adverse events among ADDERALL XR+-treated patients (3.4%) discontinued due to insonnia and one patient each for depression, motor tics, headaches, light-headed-ess, and axiey, .
In one placebo-controlled 4-week study among adults with ADHD, patients (M=33). There patients since ADDERALL XR+-treated patients (N=43) were 3.1% (n=6) for nervousness including anxiety and irritability. 2.6% (n=5) for insonnia, 1% (n=2) each for ALT increase, adjuitation, ender sevents among ADDERALL XR+-treated patients (N=13) were 3.1% (n=6) for nervousness including anxiety and irritability. 2.6% (n=5) for insonnia, 1% (n=2) each for ALT increase, adjuitation, ender sevents among ADDERALL XR+-treated patients (N=13) were 3.1% (n=6) for nervousness including anxiety and irritability. 2.6% (n=5) for insonnina, 1% (n=2) each for ALT increase, adjuitation, ender a somnolence: .
Morphetamine States
Morphetamine States
Morger events outing a countrolled triat. Adverse events reported in 3 -week clinical triat indolescents and adults, respectively, treated with ADDERALL XR+ reader the linical triats. Similarly, the clifed frequencies cannot be compared with figures obtained from othese which ADDERALL XR+ reader the clinical triats. Similarly, the clifed frequencies cannot be compared with figures obtained from othese which adverse events involving different treatments, uses, and investigators. The cited figures, however, do provide the prescriber shally and non-drug factors to the adverse event incidence at the second busines. The cited figures are than the defined form other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescriber shally a diverse event incidence at the theore figures. the states, ints with a history of drug abuse. on or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result). WARNINGS Psychosis: Clinical experience suggests that, in psychotic patients, administration amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. Long-Term Suppression of Growth: Data are inadequate to determine whether chronic used stimulants in children, including amphetamine, may be causally associated with suppression growth. Therefore, growth should be monitored during tratement, and patients who are growing or gaining weight as expected should have their treatment interrupted. Sudden Death and Pre-existing Structural Cardiac Abnormalities. Sudden death has been reported in association with KNS stimulant treatment at usual doses in children with structural cardiac abnormalities. Although some sued in children, adolescents, or adults with known structural cardiac abnormalities. PRECAUTIONS General: The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the PRECAUTIONS General: The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Hypertension: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate metrication. Sustained increases in blood pressure should be treated with dose reduction and/or appropriate medication. In a controlled 4-week outpatient clinical study of adolescents with ADHD. Isolated systolic blood pressure elevations ≥15 mmHg were observed in 7/64 (11%) placebo-treated patients and 7/100 (7%) patients receiving ADDERALL XR\* 10 or 20 mg. Isolated elevations in diasolic blood pressure ≥8 mmHg were observed in 16/64 (25%) placebo-treated patients and support and stature) were observed in 16/71 (12%) and 8/23 (35%), subjects administered 10 mg and 20 mg ADDERALL XR\*, respectively, Higher single dolescents, Isolated systolic blood pressure (above the upper 95% CI for age, gender and stature) were observed in 2/17 (12%) and 8/23 (35%), subjects administered 10 mg and 20 mg ADDERALL XR\*, respectively, Higher single dolescents, Isolation and honic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulari indeclations. **Effects on Weight**. Amphetamines have been associated with apertite. Absolute weight increases in treated children over time, but the increases are smaller than expected based on CDC normative values. These receiving 10 mg and 20 mg ADDERALL XR\*. Higher single obsective the cautomed accordingly. **Drug Interactions:** Anothetamines have been associated with apertite. Absolute weight increases in treated children over time, but the increases are smaller than expected based on CDC normative values. These receiving 10 mg at 20 mg ADDERALL XR\*. Higher single obsective sociated with aperterively for patients receiving 10 mg acorotic acid, el. Inary aciditying agents—Inese agents (ammonium chiorore, sooium acid prospirate, etc.) increase ure concentration in i onicad species of the amphetamine molecule, thereby increasing urinary excition. Both groups of agents lower blood els and efficacy of amphetamines. *Interrigic blockers* are inhibited by amphetamines. *Calmisting agents*—Gastrointestinal akalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. *Calmisting agents*—Gastrointestinal akalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. *Calmisting agents*—Gastrointestinal akalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. *Calmisting agents*—Gastrointestinal akalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. *Calmisting agents*—Gastrointestinal akalinizing agents increase blood levies and therefore potentiate the toris of amphetamines. *Calmisting agents*—Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents: *Calmisting agents*—Mol antidepressants, as well as a metabolite of furzacitone, slow amphetamine metabolism. This wing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monamines from renergic nerve endings: this can cause headances and other signs of hypertensive crisis. A variety of toxic neurological ects and malignant hyperpyrexia can occur, sometimes with fatal results. *Utilipartensives*—Amphetamines may antagonize the hypotensive effects of antihypertensives. *Utipromazine*—Chiopromazine—Dilock dopamine and norepinephrine receptors, thus inhibiting the central stimulant *esperidin*—Hambetamines, block dopamine and norepinephrine receptors, thus inhibiting the central stimulant *esperidin*—Hambetamines may delay intestinal absorption of attributed must block dopamine teceptors, thus inhibiting the central stimulant *esperidin*—Amphetamines potentiate the analgesic effect of meperidme. *Esperidin*—Amphetamines potentia ose-related adverse events te: The following events did not meet the criterion for inclusion in Table 2 but were reported by 2% to 4% of adolescent tents receiving ADDERALL XR with a higher incidence than patients receiving placebo in this study: accidental injury, henia (fatigue), dry mouth, dyspepsia, emotional lability, nausea, somnolence, and vomiting. cluded doses up to 40 mg he 3 Adverse Events Reported by 5% or More of Adults Receiving ADDERALL XR\* with Higher Incidence Than on Table 3 Adverse Events Reported by 5% or More of Adults Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study\* Halogeridol—Halogeridol block dopamine receptors, thus inhibiting the central struutant effects or ampetamines. *Uthium carbonate—*The anoretic and struutatory effects of ampetamines may be inhibited by lithium carbonate. *Meparidine—*Amphetamines potentiate the analgesic effect of meperidine. *Bayet and the structure of the analysis of the structure of ampetamines may be linhibited by lithium carbonate. Methemanine therapy—Utinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methemanine therapy. Norepinephrime—*Amphetamines enhance the adrenergic effect of norepinephrine.
*Phenobarbital—*Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.
*Proproprine—*In cases of propoxybnee overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur. *Veratrum alkaloids—*Amphetamines inhibit the hypotensive effect of veratrum alkaloids.
**DrugLaboratory Test Interactions:** Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening, Amphetamines ray infere with urnary steroid determinations.
**Carcinogenesis/Mutagenesis and Unpairment of Ferlility**: No evidence of carcinogeneity was found in studies in which d.1-amphetamine, in the enantimes ray infere and rats in the det for 2 years at doses of up to 30 mg/kg/day. and 81 times, respectively, the maximum recommended human dose of 30 mg/day (subj subject).
**Amphetamine, in the enantimum recommended human dose of 30 mg/kg/day (approximately 1-day subject). Amphetamine, in the enantimum recommended human dose of 30 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/kg/day (approximately 5 times** Note: The following events did not meet the criterion for inclusion in Table 3 but receiving ADDERALL XR<sup>®</sup> with a higher incidence than patients receiving place reaction, constipation, tooth disorder, emotional lability, libido decreased, twitching, dyspnea, sweating, dysmenorrhea, and impotence. ioria, dyski 1e, seizi Corine: Impotence, changes in libido. IG ABUSE AND DEPENDENCE ERALL XR® is a Schedule "

refrain from nursing. Pediatric Use: ADDERALL XR® is indicated for use in children 6 years of age and older. Use in Children Under Six Years of Age: Effects of ADDERALL XR® in 3-5 year olds have not been studied. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under

s of age. if **use:** ADDERALL XR<sup>®</sup> has not been studied in the geriatric population.

ADVERSE EVENTS The premarketing development program for ADDERALL XPe included exposures in a total of 1315 participants in clinical trials (635 pediatric patients, 350 adolescent patients, 248 dault patients, 82 healthy adult subjects). Of these (365 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (N+40). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and EOSs. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using

terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow. CoSTAH terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatmentent adverse event of the type listed. se events associated with discontinuation of treatment: In two placebo-controlled studies of up to 5 weeks duration arm: n with ADHD. 24% 10/4250 of ADDERALL XR® treated patients discontinued due to adverse events (including 3 patie Children With ADHD, 2.4% (10/42.c) or AUDERALL X4° treated patients discontinued due to auverse events (includ with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7259) receiving placebo. The most fre events associated with discontinuation of ADDERALL XR° in controlled and uncontrolled, multiple-dose clinical tria patients (N=556) are presented below. Over half of these patients were exposed to ADDERALL XR° for 12 months or Afverse event % of bediatric patients discussion (n=595) 2.9 1.5 1.2 1.0 0.7

Table 1 Adverse Events Reported by More Than 1% of Pediatric Patients Receiving ADDERALL XR® with Higher Incidence

Body System	Preferred Term	ADDERALL XR® (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Digestive	Loss of Appetite	22%	2%
System	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Lability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%
Metabolic/Nutritional	Weight Loss	4%	0%
Table 2 Adverse Events Rep Higher Incidence Than Place	ported by 5% or more of Adolescents Weig ebo in a 287 Patient Clinical Forced Weekly	ning $\leq$ 75 kg/165 lbs Receiving -Dose Titration Study*	ng ADDERALL XR® witi
Body System	Preferred Term	ADDERALL XR® (n=233)	Placebo (n=54)
General	Abdominal Pain (stomachache)	11%	2%
Dinestive System	Loss of Annetite b	36%	2%

DERALL XI (n=191) Placebo (n=64)

General	Asthenia	6%	5%
	Headache	26%	13%
Digestive System	Loss of Appetite	33%	3%
	Diarrhea	6%	0%
	Dry Mouth	35%	5%
	Nausea	8%	3%
Nervous System	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Insomnia	27%	13%
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	11%	0%

The following adverse reactions have been associated with amphetamine use: Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. Central Nervous System: Psycholic episodes at recommended doese, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, remork, headcathe, exacerbation of motor and phonic tics and Tourette's syn-5, stroke. Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. And may occur as undesirable effects. s. 1s including angioedema and anaphylaxis

DRUG ABUSE AND DEPENDENCE ADDEFALL XR<sup>III</sup> is a Schedule II controlled substance. Ampletamines have bene extensively abused. Tolerance, extreme psychological dependence, and severe social disabilit occurred. There are reports of patients who have increased the dosage to levels many times higher than recomm Arourd cessation following prolonged high dosage administration results in extreme fatigue and mental depression; cit are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe derma marked insomia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxicat psychosis, often clinically indistinguishable from schizophrenia.

IDOSAGE dual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low toms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyy ration .contusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomydysis. Fatigu ly follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, ension and circulatory collapse. Gastrointestimal symptoms include nerses, vomiting, diarrhea, and ab Usually follow the central mervous system stimulation. Cardiovascular effects include arrhythmas, hypertesison and circulatory couldage, Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cran Fata piosoning is usually preceded by convulsions and coma. Treatment: Consult with a Central Polyson Control Center for up to date guidance and advice. Management of acute ampletan intoxication is largely symptomatic and includes gastric lavage, administration of activate of character and polyson and sedation. Experience with hemodalysis or performed dialysis is inadequate to permit recommendation in this reg Acidification of the urine increases ampletamine excretion, but is believed to increase risk of acute renal failure if myoglobil is present. If acute severe hypertension complicates ampletamine overdosage, administration of intravenous phentolamine been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achie Chlopromazine antagonizes the central stimulant effects of ampletamines and can be used to treat ampletamine intoxicatio The prolonged release of mixed ampletamine satts from ADDERALL XR+ should be considered when treating patients with over (59-86° F) [see USP Controlled Room Temperature]. Manufactured for Stite USB Len., Wayne, PA 1908? Made in USA For more information call 1-800-828-2088, or visit www.adderalkr.com. ADDERALL\* and ADDERALL XR+ are registered in the US Patent and Trademark Office. Covorind USG006 Shire USI Inc. **Shire** 

rk Office. Copyright ©2006 Shire US Inc 381 0107 009 Rev. 2/06 ABFS15 Medical records were retrospectively evaluated for the pair from the date of vascular dementia diagnosis. The researchers assessed participant demographics and each subject's history of smoking, alcohol abuse, obesity, diabetes, stroke or transient ischemic attack, hypertension, coronary artery disease, heart failure, myocardial infarction, peripheral vascular disease, angina, pulmonary embolism/deep vein thrombosis, and other factors.

The researchers used univariate and multivariate conditional logistic regression to estimate the odds ratio for vascular dementia associated with exposure to specific risk factors and to explore interactions among the different risk factors.

In the univariate analysis, stroke, transient ischemic attack, diabetes, peripheral vascular disease, hypertension, and coronary artery disease were associated with an increased risk of vascular dementia.

In the multivariate analysis, stroke history, atrial fibrillation, and diabetes were associated with an increased risk of vascular dementia. Hypertension approached statistical significance in this model.

## Late-Life AD Risk Linked to Midlife Fat Distribution

SAN DIEGO — The increased risk of Alzheimer's disease may be more closely related to midlife distribution of adiposity rather than to being overweight or obese, according to the results of a large-scale study presented at the annual meeting of the American Academy of Neurology.

Researchers were able to use data from almost 9,000 members of the Kaiser Permanente Health Plan who underwent a series of tests between 1964 and 1973 when they were aged 40-45 years. One evaluation included measurement of skinfold thickness using calipers in the subscapular and triceps regions. Between 1994 and 2003, investigators checked medical records for diagnoses of Alzheimer's disease.

The findings showed that people in the upper 20% of adiposity in the subscapular region were almost four times more likely to develop Alzheimer's disease than were those in the lowest 20%. The risk for developing Alzheimer's disease for individuals in the upper 20% of adiposity on triceps measurements was about three and a half times greater than that of people in the lowest quintile, according to lead researcher Dr. Rachel A. Whitmer, a research scientist at the Kaiser Permanente division of research, in Oakland, Calif.

Previous research by Dr. Whitmer (BMJ 2005;330:1360) and others (Arch. Intern. Med. 2003;163:1524-8) has shown that overweight and obesity in middle age increase the future risk of dementia and Alzheimer's disease. However, these studies relied on measurement of body mass index. The data from the current study, in which calipers were used to measure skinfold, were adjusted for body mass index. -Amy Rothman Schonfeld