

# Failed Alzheimer's Trials Shift Focus to Prevention

BY MICHELE G. SULLIVAN

VIENNA — Alzheimer's drug researchers served up a string of bad news at the International Conference on Alzheimer's Disease, presenting one failed trial after another.

None of these strategies tested—blocking amyloid, improving insulin sensitivity in the brain, or even doubling up on agents that improve synaptic signaling—was able to alter the steady rate of cognitive and functional decline in patients with mild to moderate Alzheimer's, also among the failures were the omega-3 fatty acid studies.

"We are again left to wonder whether clues from epidemiology are more related to delaying or protective factors rather than factors related to progression of established disease," said Dr. Samuel Gandy, Mount Sinai Professor of Alzheimer's Disease Research at Mount Sinai Medical Center in New York.

Instead of searching for the compound that will alter the so-far inevitable decline seen in Alzheimer's, the key will probably be preventing the disease from taking hold in the first place, he said in an interview.

Among the failures was a phase II placebo-controlled trial of rosiglitazone that showed no benefit on cognition in a group of 553 patients with mild to moderate Alzheimer's.

The 24-week trial, sponsored by GlaxoSmithKline, randomized the patients (mean age 72 years) to placebo, a positive control group of donepezil 10 mg/day, or one of two rosiglitazone doses (2 mg or 8 mg daily). The extended-release formulation was an experimental one, and not the Food and Drug Administration-approved Avandia, Dr. Michael Gold said at the meeting.

The study examined each treatment's effect in the overall cohort, on those who were apolipoprotein E e4 (APOE e4) negative, and all subjects except those homozygous for the high-risk gene. The primary end points were changes in the Alzheimer's Disease Assessment Scale—cognitive domain (ADAS-cog) and Clinicians' Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus).

At 24 weeks, neither of the rosiglitazone doses was significantly different from placebo in either cognitive assessment for any of the populations. But in the overall population and in the group that included everyone except the APOE e4 homozygous carriers, CIBIC scores were significantly better for those on donepezil than for those taking placebo.

Since that finding had not been adjusted for covariates, "I don't think it's anything we can hang our hats on," said Dr. Gold, global clinical vice president of neurology at GlaxoSmithKline, Durham, N.C.

Dr. Gordon Wilcock reported another failed phase III trial for tarenflurbil, this one conducted in the United

States, Canada, and Western Europe. In 2008, tarenflurbil, a selective amyloid-lowering agent, failed its highly anticipated phase III U.S. trial.

"With two failed phase III trials, tarenflurbil has killed itself off completely," Dr. Wilcock, of the University of Oxford (England), said at the meeting.

Tarenflurbil was the first gamma secretase modulator to be tested in a phase III trial. This class of drug is thought to reduce the levels of toxic amyloid beta (Aβ<sub>42</sub>) in the brain by changing the point at which the enzyme gamma secretase cuts the amyloid precursor protein, shifting the ratio to less of the toxic Aβ<sub>42</sub> and more of the less-toxic Aβ<sub>40</sub>.

The most recent trial failed to show statistically significant or clinically meaningful changes in any of the three outcomes it assessed: Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-cog), ADAS-activities of daily living (ADAS-ADL), or the Clinical Dementia Rating—sum of boxes (CDR-sb).

"This was a well-powered, well-designed, and well-conducted trial," that would have identified any benefit that existed, Dr. Wilcock said. Its message seems to be that researchers should investigate non-amyloid-centered therapies. The trial was sponsored by Myriad Pharmaceuticals Inc. of Salt Lake City, for which Dr. Wilcock is a consultant.

Finally, a combination of two drugs already proven effective in Alzheimer's disease worked no better than a single agent to slow the disorder's cognitive and functional decline, reported Dr. Oliver Peters of Charité University Hospital Berlin.

He presented results of a randomized, controlled trial of a combination of galantamine and memantine compared to galantamine alone in 233 patients with mild-moderate Alzheimer's. The patients (mean age 72 years) were naive to cholinesterase inhibitors and memantine. They were randomized to 24 mg of galantamine daily plus a placebo, or a combination of 24 mg galantamine and 20 mg memantine for 1 year. The primary end points were the ADAS-cog, ADAS-ADL, and CDR-sb.

The combination was well tolerated, but the addition of memantine did not significantly affect any of the clinical end points. "At 16 weeks, we saw a little better effect in the combination group," on all three measures, although none of the differences were statistically significant, Dr. Peters said. After 16 weeks, patients in both arms experienced steady declines which, by week 52, were significantly worse than their baseline scores. APOE e4 status had no significant impact on the results.

Dr. Peters acknowledged that a larger group would have been preferable. Janssen-Cilag of Buckinghamshire, England, which sponsored the trial, thought that the study was sufficiently powered, he said, adding that he had no financial relationship with the company. ■

manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

**Respiratory System:** Frequent were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

**Skin and Appendages:** Frequent were rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

**Special Senses:** Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

**Urogenital System:** Frequent were dysmenorrhea\*; infrequent were albuminuria, amenorrhea\*, breast pain\*, cystitis, dysuria, prostatitis\*, urinary retention; rare were breast enlargement\*, breast neoplasm\*, female lactation, hematuria, kidney calculus, metrorrhagia\*, nephritis, nocturia, pregnancy and puerperal disorders\*, salpingitis, urinary incontinence, uterine fibroids enlarged\*; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

\*Based on the number of men and women as appropriate.

**Post-Marketing Reports:** Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertension, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including Torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

**DRUG ABUSE AND DEPENDENCE: Controlled Substance Class:** Paroxetine hydrochloride is not a controlled substance.

**Physical and Psychological Dependence:** Paroxetine hydrochloride extended-release tablets have not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of paroxetine hydrochloride extended-release tablets (e.g., development of tolerance, incrementations of dose, drug seeking behavior).

**OVERDOSAGE: Human Experience:** Since the introduction of immediate-release paroxetine hydrochloride in the United States, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 nonfatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including Torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

**Overdosage Management:** Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for paroxetine are known.

A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS: Drug Interactions: *Drugs Metabolized by Cytochrome CYP2D6*).

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

**DOSE AND ADMINISTRATION: Major Depressive Disorder: Usual Initial Dosage:** Paroxetine hydrochloride extended-release tablets should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials demonstrating the effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 25 mg dose may benefit from dose increases, in 12.5 mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least one week.

Patients should be cautioned that paroxetine hydrochloride extended-release tablets should not be chewed or crushed, and should be swallowed whole.

**Maintenance Therapy:** There is no body of evidence available to answer the question of how long the patient treated with paroxetine hydrochloride extended-release tablets should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has shown that efficacy is maintained for periods of up to one year with doses that averaged about 30 mg, which corresponds to a 37.5 mg dose of paroxetine hydrochloride extended-release tablets, based on relative bioavailability considerations (see CLINICAL PHARMACOLOGY: Pharmacokinetics in full prescribing information).

**Special Populations: Treatment of Pregnant Women During the Third Trimester:** Neonates exposed to paroxetine hydrochloride extended-release tablets and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

**Dosage for Elderly or Debilitated Patients, and Patients with Severe Renal or Hepatic Impairment:** The recommended initial dose of paroxetine hydrochloride extended-release tablets is 12.5 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 50 mg/day.

**Switching Patients to or From a Monoamine Oxidase Inhibitor:** At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with paroxetine hydrochloride extended-release tablets. Similarly, at least 14 days should be allowed after stopping paroxetine hydrochloride extended-release tablets before starting an MAOI.

**Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets:** Symptoms associated with discontinuation of immediate-release paroxetine hydrochloride or paroxetine hydrochloride extended-release tablets have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine hydrochloride extended-release tablets are being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.



Mylan

Mylan Pharmaceuticals Inc.  
Morgantown, WV 26505

REVISED FEBRUARY 2009  
BS-PRXT:R6mc

Page 3 of 3