



Brains of patients taking both insulin and oral hypoglycemic drugs had fewer plaques (white arrows) than those of nondiabetics, but equal neurofibrillary tangles (black).

COURTESY DR. VAHRAH HAROUTUNIAN

Insulin Tied to Fewer Plaques in AD

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CHICAGO — A postmortem analysis of subjects with both Alzheimer's disease and diabetes found up to 80% fewer amyloid β plaques in the brains of those who took both insulin and oral diabetic medication while alive.

The finding might shed some light on a discrepancy that has puzzled Alzheimer's researchers: Although epidemiological

studies confirm a significantly increased risk of Alzheimer's and other dementias in subjects with diabetes, their brains generally appear less physically ravaged by the disease, Michal Schnaider Beerli, Ph.D., said at the International Conference on Alzheimer's Disease.

"Medication might be one explanation for this apparent discrepancy between [epidemiological] and neuropathology studies," said Dr. Beerli of the Mount Sinai School of Medicine, New York.

The study involved 148 brains from the Mount Sinai School of Medicine brain bank. All were from subjects with Alzheimer's disease, half of whom also had diabetes. The subjects were matched for age (mean age, 81 years), sex (57% female), and dementia severity (mean clinical dementia rating score, 2.4).

Dr. Beerli and her colleagues divided the subjects according to use of diabetic medications. Of the 124 subjects with diabetes, 49 were on insulin only, 28 were on oral diabetes medications only, 18 were on a combination of agents, and 29 weren't on medications. The groups were compared with each other and with those without diabetes.

The researchers saw no significant links



The link between diabetes drugs (like insulin) and fewer plaques echos the effects of both on insulin neurobiology.

DR. BEERLI

between medication and the presence of tau neurofibrillary tangles. But they found a strong interaction between medication and amyloid β_{42} plaques—a diagnostic hallmark of Alzheimer's—in the hippocampus, amygdala, and entorhinal cortex.

Plaque presence was rated from 0 (none) to 2 (severe). Subjects without diabetes had a rating of about 1.5, as did those with diabetes who were taking only oral medications. Diabetics who took no diabetes medications had a rating of about 1.25. Subjects taking insulin had a lower, but not significantly lower, plaque rating (1, considered sparse), compared with those without diabetes, diabetics not on medications, and those on only oral agents, Dr. Beerli said.

The largest differences were between subjects on combination therapy (insulin and oral medications) and those who took only oral agents and subjects without diabetes. Combination therapy subjects had a plaque rating of about 0.25, or 80% lower than ratings for subjects in the other two groups. Those who had taken combination therapy also had significantly fewer plaques than did those who took no medications, as well as those who took only insulin.

These relationships remained significant even after controlling for age at death, sex, dementia severity, fasting glucose level at last admission, and apo E4 status. There were no significant changes when subjects with other comorbidities were excluded.

"The results suggest insulin combined with other diabetes medication is associated with a substantial reduction in brain neuritic plaque density, consistent with the effects of both on the neurobiology of insulin," Dr. Beerli said at the meeting, which was presented by the Alzheimer's Association. "Insulin and insulin sensitizers (oral hypoglycemics) target organs at the periphery but also seem to have an effect on the brain, [suggesting] the possibility of therapeutic targeting of insulin signaling pathways of the brain for reducing amyloid β -associated neuropathology of Alzheimer's." ■

and altered neurological development of female offspring were observed when dams were treated with 4 times the MRHD.

8.3 Nursing Mothers

Ropinirole inhibits prolactin secretion in humans and could potentially inhibit lactation.

Ropinirole has been detected in the milk of lactating rats. Although many drugs are excreted in human milk, transfer of ropinirole into human milk has not been demonstrated. Due to the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of ropinirole to the mother.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

8.5 Geriatric Use

Dosage adjustment is not necessary in the elderly (above 65 years), as the dose of REQUIP XL is to be individually titrated to clinical response [see *Clinical Pharmacology (12.3) of the full prescribing information*]. Pharmacokinetic studies conducted in patients demonstrated that oral clearance of ropinirole is reduced by 15% in patients above 65 years of age compared to younger patients.

Of the total number of patients who participated in clinical trials of REQUIP XL for Parkinson's disease, 387 patients were 65 and over and 107 patients were 75 and over. Among patients receiving REQUIP XL, hallucination was more common in elderly subjects (10%) compared with non-elderly subjects (2%). The incidence of overall adverse events increased with increasing age for both patients receiving REQUIP XL and placebo.

8.6 Renal Impairment

No dosage adjustment of ropinirole is needed in patients with moderate renal impairment (creatinine clearance of 30 to 50 mL/min). The use of ropinirole in patients with severe renal impairment has not been studied.

8.7 Hepatic Impairment

The pharmacokinetics of ropinirole have not been studied in patients with hepatic impairment. Since patients with hepatic impairment may have higher plasma levels and lower clearance, ropinirole should be titrated with caution in these patients.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Ropinirole is not a controlled substance.

9.3 Dependence

Animal studies and human clinical trials with ropinirole did not reveal any potential for drug-seeking behavior or physical dependence.

10 OVERDOSAGE

10.1 Human Overdose Experience

In the Parkinson's disease program, there have been patients who accidentally or intentionally took more than their prescribed dose of ropinirole. The largest overdose reported with immediate-release ropinirole in clinical trials was 435 mg taken over a 7-day period (62.1 mg/day). Of patients who received a dose greater than 24 mg/day, reported symptoms included adverse events commonly reported during dopaminergic therapy (nausea, dizziness), as well as visual hallucination, hyperhidrosis, claustrophobia, chorea, palpitations, asthenia, and nightmares. Additional symptoms reported for doses of 24 mg or less or for overdoses of unknown amount included vomiting, increased coughing, fatigue, syncope, vasovagal syncope, dyskinesia, agitation, chest pain, orthostatic hypotension, somnolence, and confusional state.

10.2 Overdose Management

The symptoms of overdose with ropinirole are generally related to its dopaminergic activity; these symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide. General supportive measures are recommended. Vital signs should be maintained, if necessary. Removal of any unabsorbed material (e.g., by gastric lavage) may be considered.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in Charles River CD-1 mice at doses of 5, 15, and 50 mg/

kg/day and in Sprague-Dawley rats at doses of 1.5, 15, and 50 mg/kg/day (top doses which, based on mg/m², are equivalent to 10 and 20 times, respectively, the MRHD of 24 mg/day). In the male rat, there was a significant increase in testicular Leydig cell adenomas at all doses tested, i.e., ≥ 1.5 mg/kg (0.6 times the MRHD on a mg/m² basis). This finding is of questionable significance because the endocrine mechanisms believed to be involved in the production of Leydig cell hyperplasia and adenomas in rats are not relevant to humans. In the female mouse, there was an increase in benign uterine endometrial polyps at a dose of 50 mg/kg/day (10 times the MRHD on a mg/m² basis).

Ropinirole was not mutagenic or clastogenic in the *in vitro* Ames test, the *in vitro* chromosome aberration test in human lymphocytes, the *in vitro* mouse lymphoma (L1578Y cells) assay, and the *in vivo* mouse micronucleus test.

When administered to female rats prior to and during mating and throughout pregnancy, ropinirole caused disruption of implantation at doses of 20 mg/kg/day (8 times the MRHD on a mg/m² basis) or greater. This effect is thought to be due to the prolactin-lowering effect of ropinirole. In humans, chorionic gonadotropin, not prolactin, is essential for implantation. In rat studies using low doses (5 mg/kg) during the prolactin-dependent phase of early pregnancy (gestation days 0 to 8), ropinirole did not affect female fertility at dosages up to 100 mg/kg/day (40 times the MRHD on a mg/m² basis). No effect on male fertility was observed in rats at dosages up to 125 mg/kg/day (50 times the MRHD on a mg/m² basis).

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling in full prescribing information (17.9)

Physicians should instruct their patients to read the Patient Information leaflet before starting therapy with REQUIP XL and to reread it upon prescription renewal for new information regarding the use of REQUIP XL.

17.1 Dosing Instructions

Patients should be instructed to take REQUIP XL only as prescribed. If a dose is missed, patients should be advised not to double their next dose.

REQUIP XL can be taken with or without food. Taking REQUIP XL with food may reduce the occurrence of nausea [see *Dosage and Administration (2.1)*].

REQUIP XL Tablets should be swallowed whole. They should not be chewed, crushed, or divided [see *Dosage and Administration (2.1)*].

Ropinirole is the active ingredient that is in both REQUIP XL and REQUIP Tablets (the immediate-release formulation). Ask your patient if they are taking another medication containing ropinirole.

17.2 Postural (Orthostatic) Hypotension

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating. Hypotension and/or orthostatic symptoms may occur more frequently during initial therapy or with an increase in dose at any time (cases have been seen after weeks of treatment). Accordingly, patients should be cautioned against standing up rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with REQUIP XL [see *Warnings and Precautions (5.2, 5.3)*].

17.3 Elevation of Blood Pressure and Changes in Heart Rate

Patients should be alerted to the possibility of increases in blood pressure during treatment with REQUIP XL. Exacerbation of hypertension may occur. Medication dose adjustment may be necessary if elevation of blood pressure is sustained over multiple evaluations. Patients with cardiovascular disease, who may not tolerate marked changes in heart rate, should also be alerted to the possibility that they may experience significant increases or decreases in heart rate during treatment with REQUIP XL [see *Warnings and Precautions (5.4)*].

17.4 Sedating Effects

Patients should be alerted to the potential sedating effects caused by REQUIP XL, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse reaction with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with REQUIP XL to gauge whether or not it affects their mental

and/or motor performance adversely. Patients should be advised that if increased somnolence or episodes of falling asleep during activities of daily living (e.g., conversations, eating, driving a motor vehicle, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician.

Because of possible additive effects, caution should be advised when patients are taking other sedating medications, alcohol, or other CNS depressants (e.g., benzodiazepines, antipsychotics, antidepressants, etc.) in combination with REQUIP XL or when taking concomitant medications that increase plasma levels of ropinirole (e.g., ciprofloxacin) [see *Warnings and Precautions (5.1)*].

17.5 Hallucinations

Patients should be informed they may experience hallucinations (unreal visions, sounds, or sensations) while taking ropinirole. The elderly are at greater risk than younger patients with Parkinson's disease; and the risk is greater in patients who are taking ropinirole with L-dopa or taking higher doses of ropinirole, and may also be further increased in patients taking any other drugs that increase dopaminergic tone [see *Warnings and Precautions (5.5)*].

17.6 Impulse Control Symptoms Including Compulsive Behaviors

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone, that are generally used for the treatment of Parkinson's disease or Restless Legs Syndrome, including ropinirole. In the clinical development program (N = 613), 6 patients treated with REQUIP XL exhibited compulsive behaviors consisting of pathological gambling and/or hypersexuality. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with REQUIP XL. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking REQUIP XL. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking REQUIP XL.

17.7 Nursing Mothers

Because of the possibility that ropinirole may be excreted in breast milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother [see *Use in Specific Populations (8.3)*].

Patients should be advised that ropinirole could inhibit lactation, as ropinirole inhibits prolactin secretion.

17.8 Pregnancy

Because ropinirole has been shown to have adverse effects on embryo-fetal development, including teratogenic effects, in animals, and because experience in humans is limited, patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy [see *Use in Specific Populations (8.1)*].

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References: 1. Tompson DJ, Vearer D. Steady-state pharmacokinetic properties of a 24-hour prolonged-release formulation of ropinirole: results of two randomized studies in patients with Parkinson's disease. *Clin Ther*. 2007;29(12):2654-2666. 2. Pahwa R, Stacy MA, Factor SA, et al, on behalf of the EASE-PD Adjuvant Study Investigators. Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. *Neurology*. 2007;68(14):1108-1115.

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