

WHI Low-Fat Diet Flawed; Some Benefit Shown

BY MITCHEL L. ZOLER
Philadelphia Bureau

BETHESDA, MD. — The biggest problem with the diet modification study of the Women's Health Initiative was the diet. Not enough women stuck with it, and it had an outdated design.

Despite these flaws, the trial's results, first reported in February, came close to proving that a reduced-fat diet—followed by thousands of postmenopausal women

for an average of 8.1 years—could significantly reduce the incidence of invasive breast cancer.

"It's not an optimal diet; it's not feasible" for many women, commented Dr. JoAnn E. Manson at a conference on the Women's Health Initiative sponsored by the Department of Health and Human Services. The average level of fat reduction that most women achieved in their diet was not as substantial as had been planned, blunting the diet's effects.

Despite this shortcoming, the results showed "signals" that a low-fat diet produced some benefits, including a trend toward a reduced number of invasive breast cancers, a bigger reduction in breast cancers among women who had the highest level of fat in their diet at baseline, and a reduction in the incidence of colonic polyps or adenomas, said Dr. Manson, chief of the division of preventive medicine at Brigham and Women's Hospital, Boston, and a principal investigator for the WHI.

The study failed to show that the reduced-fat diet with increased consumption of fruits, vegetables, and grains could lower the incidence of cardiovascular disease.

"You need a 20%-30% decrease in low-density lipoprotein cholesterol to get an effect" on cardiovascular disease. "In this study, the effect was way too low," commented Dr. Lewis H. Kuller, professor of epidemiology at the University of Pittsburgh and a principal investigator for the WHI. The diet was also "too low in polyunsaturated fats. You blunt the LDL effect by reducing polyunsaturated fats," he said in an interview.

In this respect, the diet reflected what was known when it was designed in the early 1990s. Today, researchers have a better understanding of the benefit of polyunsaturated fat for cardiovascular disease and of the danger from saturated fat.

The diet modification study of the WHI was a companion to the hormone therapy study, as well as a third study that assessed the effect of calcium and vitamin D supplements.

All three of the studies enrolled women who were postmenopausal and aged 50-79 years at entry.

The diet modification study involved more than 48,000 women

who, on their usual diet, got 32% or more of their calories from fat, based on a food frequency questionnaire, and who had no history of breast or colorectal cancer. More than 19,000 women were randomized to an intensive behavior-modification program designed to change their eating habits so that their fat intake would be no more than 20% of calories, their consumption of fruits and vegetables would be at least five servings a day, and their consumption of grains would be at least six servings daily. This diet did not involve a reduction in total calorie intake and had no weight loss goals. The more than 29,000 women randomized to the control arm were not asked to make any changes in their diet.

The diet intervention was modestly successful. One year into the study, average fat intake by women in the intervention group was 24% of daily calories. After 1 year of the study, 31% of women in the intervention group had met the goal of consuming 20% or less of their daily calories as fat. In the sixth year of the study, 14% of women in the intervention group were at this goal level. In addition, differences were modest between the intervention and control groups in the consumption of fruits, vegetables, and grains. One year into the study, women in the intervention group ate an average of 5.1 servings of fruits and vegetables daily and an average of 5.1 grain servings a day. The daily averages for women in the control group

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BRIEF SUMMARY

ZOFRAN® (ondansetron hydrochloride) Tablets ZOFRAN ODT® (ondansetron) Orally Disintegrating Tablets ZOFRAN® (ondansetron hydrochloride) Oral Solution

The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS

ZOFRAN Tablets, ZOFRAN ODT Orally Disintegrating Tablets, and ZOFRAN Oral Solution are contraindicated for patients known to have hypersensitivity to the drug.

WARNINGS

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT₃ receptor antagonists.

PRECAUTIONS

Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distension.

Information for Patients: Phenylketonurics: Phenylketonuric patients should be informed that ZOFRAN ODT Orally Disintegrating Tablets contain phenylalanine (a component of aspartame). Each 4-mg and 8-mg orally disintegrating tablet contains <0.03 mg phenylalanine.

Patients should be instructed not to remove ZOFRAN ODT Tablets from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should be gently removed and immediately placed on the tongue to dissolve and be swallowed with the saliva. Peelable illustrated stickers are affixed to the product carton that can be provided with the prescription to ensure proper use and handling of the product.

Drug Interactions: Ondansetron does not itself appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver (see CLINICAL PHARMACOLOGY, Pharmacokinetics in full prescribing information). Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. On the basis of available data, no dosage adjustment is recommended for patients on these drugs. **Phenylethylamine, Carbamazepine, and Rifampicin:** In patients treated with potent inducers of CYP3A4 (i.e., phenylethylamine, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs. **Tramadol:** Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small studies indicate that ondansetron may be associated with an increase in patient controlled administration of tramadol. **Chemotherapy:** Tumor response to chemotherapy in the P-388 mouse leukemia model is not affected by ondansetron. In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover study in 76 pediatric patients, I.V. ondansetron did not increase blood levels of high-dose methotrexate.

Use in Surgical Patients: The coadministration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg/day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg/day did not affect fertility or general reproductive performance of male and female rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing woman.

Pediatric Use: Little information is available about dosage in pediatric patients 4 years of age or younger (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections of full prescribing information for use in pediatric patients 4 to 18 years of age).

Geriatric Use: Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting in US- and foreign-controlled clinical trials, for which there were subgroup analyses, 938 were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of 65 (see CLINICAL PHARMACOLOGY section of full prescribing information).

ADVERSE REACTIONS

The following have been reported as adverse events in clinical trials of patients treated with ondansetron, the active ingredient of ZOFRAN. A causal relationship to therapy with ZOFRAN has been unclear in many cases.

Chemotherapy-Induced Nausea and Vomiting: The adverse events in Table 1 have been reported in ≥5% of adult patients receiving a single 24-mg ZOFRAN Tablet in 2 trials. These patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens (cisplatin dose ≥50 mg/m²).

Table 1. Principal Adverse Events in US Trials: Single Day Therapy With 24-mg ZOFRAN Tablets (Highly Emetogenic Chemotherapy)

Event	Ondansetron 24 mg q.d. n = 300	Ondansetron 8 mg b.i.d. n = 124	Ondansetron 32 mg q.d. n = 117
Headache	33 (11%)	16 (13%)	17 (15%)
Diarrhea	13 (4%)	9 (7%)	3 (3%)

The adverse events in Table 2 have been reported in ≥5% of adults receiving either 8 mg of ZOFRAN Tablets 2 or 3 times a day for 3 days or placebo in 4 trials. These patients were receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based regimens.

Table 2. Principal Adverse Events in US Trials: 3 Days of Therapy With 8-mg ZOFRAN Tablets (Moderately Emetogenic Chemotherapy)

Event	Ondansetron 8 mg b.i.d. n = 242	Ondansetron 8 mg t.i.d. n = 415	Placebo n = 262
Headache	58 (24%)	113 (27%)	34 (13%)
Malaise/fatigue	32 (13%)	37 (9%)	6 (2%)
Constipation	22 (9%)	26 (6%)	1 (<1%)
Diarrhea	15 (6%)	16 (4%)	10 (4%)
Dizziness	13 (5%)	18 (4%)	12 (5%)

Central Nervous System: There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron.

Hepatic: In 723 patients receiving cyclophosphamide-based chemotherapy in US clinical trials, AST and/or ALT values have been reported to exceed twice the upper limit of normal in approximately 1% to 2% of patients receiving ZOFRAN Tablets. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur. The role of cancer chemotherapy in these biochemical changes cannot be clearly determined.

There have been reports of liver failure and death in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

Integumentary: Rash has occurred in approximately 1% of patients receiving ondansetron.

Other: Rare cases of anaphylaxis, bronchospasm, tachycardia, angina (chest pain), hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures have been reported. Except for bronchospasm and anaphylaxis, the relationship to ZOFRAN was unclear.

Radiation-Induced Nausea and Vomiting: The adverse events reported in patients receiving ZOFRAN Tablets and concurrent radiotherapy were similar to those reported in patients receiving ZOFRAN Tablets and concurrent chemotherapy. The most frequently reported adverse events were headache, constipation, and diarrhea.

Postoperative Nausea and Vomiting: The adverse events in Table 3 have been reported in ≥5% of patients receiving ZOFRAN Tablets at a dosage of 16 mg orally in clinical trials. With the exception of headache, rates of these events were not significantly different in the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

Table 3. Frequency of Adverse Events From Controlled Studies With ZOFRAN Tablets (Postoperative Nausea and Vomiting)

Adverse Event	Ondansetron 16 mg (n = 550)	Placebo (n = 531)
Wound problem	152 (28%)	162 (31%)
Drowsiness/sedation	112 (20%)	122 (23%)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Bradycardia	32 (6%)	30 (6%)
Shiver(s)	28 (5%)	30 (6%)
Urinary retention	28 (5%)	18 (3%)
Hypotension	27 (5%)	32 (6%)
Pruritus	27 (5%)	20 (4%)

Preliminary observations in a small number of subjects suggest a higher incidence of headache when ZOFRAN ODT Orally Disintegrating Tablets are taken with water, when compared to without water.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of oral formulations of ZOFRAN. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ZOFRAN.

General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable ondansetron.

Hepatobiliary: Liver enzyme abnormalities

Lower Respiratory: Hiccups

Neurology: Oculogyric crisis, appearing alone, as well as with other dystonic reactions

Skin: Urticaria

Special Senses: Eye Disorders: Rare cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness generally resolved within 20 minutes.

DRUG ABUSE AND DEPENDENCE

Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

OVERDOSAGE

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual intravenous doses as large as 150 mg and total daily intravenous doses as large as 252 mg have been inadvertently administered without significant adverse events. These doses are more than 10 times the recommended daily dose.

In addition to the adverse events listed above, the following events have been described in the setting of ondansetron overdose: "Sudden blindness" (amaurosis) of 2 to 3 minutes' duration plus severe constipation occurred in 1 patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg of ZOFRAN Tablets. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the events resolved completely.



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ZOFRAN Tablets and Oral Solution:
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ZOFRAN ODT Orally Disintegrating Tablets:
Manufactured for GlaxoSmithKline
Research Triangle Park, NC 27709
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June 2005 RL-2198

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Printed in USA.

Z03482R0

December 2005

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Not the Best Candidates for Trial

WHI Data from page 1

said Dr. Johnson, a professor of medicine at Ohio State University, Columbus, and a principal investigator of the WHI.

After the WHI's calcium and vitamin D study was designed, it was piggy-backed onto the two other studies that had already begun, the hormone therapy and diet modification trials.

More than 36,000 women who were already enrolled in one or both of these ongoing WHI studies were randomized to get a daily supplement of 500 mg elemental calcium and 200 IU vitamin D or placebo, and the participants were followed for an average of 7 years.

The enrollment criteria did not contain exclusions based on calcium and vitamin D intake, and it specifically allowed women to take additional supplements of up to 1,000 mg calcium and 600 IU vitamin D per day.

At baseline, before the study began, one third of the enrolled women had a total daily calcium intake of at least 1,200 mg calcium, and another 45% of women had a daily intake of at least 1,000 mg, which meant that 78% of the participants already had a sufficient supply and were "probably not the best candidates for a calcium supplement trial," said Joan A. McGowan, Ph.D., director of the musculoskeletal diseases branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

The study's primary end point was the incidence of hip fractures, with a secondary end point of incidence of all fractures. The incidence of hip fractures was 0.14% in the supplement group and 0.16% in the placebo group, a relative proportional reduction of 12%, which was not statistically significant (N. Engl. J. Med. 2006;354:669-83).

The incidence of all fractures was 1.64% and 1.70% in the intervention and placebo groups, respectively, also a

nonsignificant difference.

These analyses were done on an intention-to-treat basis. During the first 3 years of the study, 60%-63% of women were adherent to the regimen, taking at least 80% of their assigned supplements. By the end of the study, 59% were still taking at least 80%.

A secondary analysis that focused only on the adherent participants showed that the incidence of hip fracture was 29% lower in the women taking calcium and vitamin D, compared with the placebo group, a statistically significant difference.

Another secondary analysis focused exclusively on women aged 60 or older, the group at highest risk of fracture. In this subgroup, the risk of hip fracture was 21% lower in the women in the active treatment arm, also a significant difference.

"We believe that this is strong enough information to support a role for calcium and vitamin D in reducing fracture risk," said Dr. Jackson in an interview at the meeting.

Calcium's main adverse effect was a 17% increased risk of having kidney stones, a significant difference.

"Although there was an increased risk of [developing] kidney stones, the possible benefits of calcium with vitamin D supplementation for the risk of fracture cannot be totally ignored," Dr. Joel S. Finkelstein, an endocrinologist at Massachusetts General Hospital, Boston, wrote in an editorial that accompanied the published findings (N. Engl. J. Med. 2006;354:750-2).

Dr. Finkelstein also commented in his editorial that "calcium with vitamin D supplementation by itself is not enough to ensure optimal bone health.

"Additional therapy with agents that have been proved to reduce the risk of fracture in women with osteoporosis, such as antiresorptive medications or teriparatide, may be indicated." ■

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were 3.9 servings and 4.2 servings, respectively.

The study's primary outcome was the incidence of invasive breast cancer, which was reduced by a relative 9% in the intervention group, compared with the control arm, a nonsignificant difference with a *P* value of .07 (JAMA 2006;295:629-42). Two secondary outcomes of the study were the rates of invasive colorectal cancer and cardiovascular disease. These rates did not significantly differ between the two study groups.

Researchers who ran the trial noted that the average follow-up was 8.1 years instead of the planned 9 years, a reduction caused by slower than expected recruitment of women into the study. The shortened follow-up limited the study's power to show a statistically significant difference in breast cancer rates.

But others said that even if the difference eventually becomes statistically significant with longer follow-up, the clinical importance of the reduction was questionable because the low-fat diet

was linked with three fewer cases of invasive breast cancer for every 10,000 women followed per year.

"Even if a breast cancer effect is there, it's extremely small," said Dr. Kuller at the conference. For understanding the biology of breast cancer, proving a link to dietary fat intake is very important, "but it's a very modest clinical effect."

By contrast, Ross L. Prentice, Ph.D., lead investigator for the breast cancer analysis, said that even this small impact on breast cancer incidence is clinically meaningful. Because of the lag time in the development of breast cancer, it might take many years to see the full benefits of a reduced-fat diet, he said in an interview.

The difference in breast cancer incidence could become substantial if a reduced-fat diet was maintained over a lifetime, said Dr. Prentice, a professor of biostatistics at the University of Washington, Seattle, and a researcher at the Fred Hutchinson Cancer Research Center. "A low-fat diet is a reasonable choice for overall health, but we have not yet addressed what's the best diet to recommend." ■

HT for Hot Flashes Didn't Improve Quality of Life

BY MITCHEL L. ZOLER
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BETHESDA, MD. — Now that results from the Women's Health Initiative have shot down hormone therapy as a way to prevent coronary events, dementia, and urinary incontinence in postmenopausal women, the only indication left standing has been relief of menopausal symptoms, especially vasomotor symptoms such as hot flashes.

But even this application is on shaky ground, thanks again to results from the Women's Health Initiative (WHI).

One problem with using estrogen plus progestin, or estrogen alone to manage vasomotor symptoms is that a comprehensive quality-of-life assessment in the WHI showed no clinically significant benefit from hormone therapy, Jennifer Hays, Ph.D., said at a conference on the Women's Health Initiative, sponsored by the Department of Health and Human Services. This result carries the caveat that the WHI hormone study enrolled only women who were willing to accept randomization to placebo, which means that women with the worst symptoms were probably not included.

A second problem is that 56% of women in the WHI who had hot flashes when they started hormone therapy experienced a recurrence 8-12 months after stopping hormone therapy.

The finding that symptoms recurred after hormone therapy stopped is "very important," said Dr. Hays, a developmental psychologist at Scott & White Hospital in Temple, Tex., and a principal investigator for WHI. "We now talk about treating women with estrogen for a short term, but what happens when women get taken off?"

Despite this drawback, hormone therapy is "clearly still the best treatment for vasomotor symptoms," commented Dr. Robert Brzyski, an ob.gyn. at the University of Texas Health Science Center, San Antonio, and another WHI principal investigator.

The prevalence of menopausal symptoms when women entered the WHI hormone study was related to age. Among women aged 50-54 years, the most common symptom was hot flashes, reported by about 23% of women. Vaginal dryness, headache, and mood swings were each reported by 10%-15% of women, and joint pain was noted by 20%. The prevalence of all symptoms at entry, except joint pain, was lower with increased age. For example, among women aged 55-59 years, the prevalence of hot flashes was 15%.

After 1 year of treatment with estrogen

and progestin, about 85% of women with hot flashes reported that this symptom had significantly improved, compared with about 58% of women in the placebo group, a statistically significant difference. Improvement in vaginal dryness was reported by about 75% of women treated with estrogen plus progestin, compared with about 55% in the placebo group, also a significant difference, Dr. Hays said at the meeting.

But serial surveys that measured health-related quality of life using the RAND 36-Item Health Survey failed to identify any clinically meaningful improvement after 1 or 3 years of estrogen-

Despite this drawback, hormone therapy is 'clearly still the best treatment for vasomotor symptoms,' according to one WHI principal investigator.

plus-progestin treatment, compared with placebo. A similar quality-of-life assessment using the RAND 36 failed to show any clinically meaningful improvements in women treated with estrogen only, compared with placebo.

The incidence of menopausal symptoms in women who stop hormone therapy was examined by studying the 9,351 women who were still taking their prescribed estrogen plus progestin or placebo regimen when the treatment phase of this trial was stopped in July 2002.

This group constituted 56% of the participants originally enrolled, and included 4,558 in the hormone arm and 4,793 in the placebo group.

During the first 8-12 months after stopping, hot flashes occurred in 56% of women who had this symptom when they began hormone therapy, compared with a 21% incidence in women who had hot flashes when they entered the placebo arm of the study (JAMA 2005;294:183-93). In women who had hot flashes at any time before entering the WHI study, the symptom occurred after treatment stopped in 22% of women who had been on estrogen plus progestin vs. 4% of women from the placebo group.

The results suggest that hormone therapy only postpones certain menopausal symptoms, and it may eventually make the symptoms worse, said Dr. Hays in an interview.

Several management options are alternatives to hormone therapy for menopausal symptoms, including drugs such as clonidine or selective serotonin reuptake inhibitors, treatment with various supplements or herbal agents, or modified forms of hormone therapy that involve different dosages, duration of treatment, hormone formulations, or routes of administration. But these alternatives are all limited by a lack of information on their safety and efficacy, said Dr. Margery Gass, an ob.gyn. at the University of Cincinnati and a principal investigator for the WHI.