Baseline Anxiety Affects Adjustment to Cancer

BY HEIDI SPLETE

Senior Writer

7omen who feel chronic anxiety or suppress anxiety in daily life are more likely to be traumatized by a diagnosis of breast cancer, compared with those who are generally less anxious, said Yumi Iwamitsu, Ph.D., of Kitasato University, Kanagawa, Japan, and colleagues.

The investigators examined the differences in emotional responses among 21

women who had received a diagnosis of breast cancer and 72 women who had benign tumors. Their mean age was 46 years.

Each woman completed the Profile of Mood States (POMS), the Courtauld Emotional Control Scale, and the Manifest Anxiety Scale during a first visit to an outpatient clinic for a breast biopsy (Psychosomatics 2005;46:19-24). They completed the POMS again after a second visit at which they learned the biopsy results.

Both the breast cancer patients and be-

nign tumor patients were assigned to either low anxiety or high anxiety subgroups based on the Manifest Anxiety Scale scores, and either negative emotion suppression or negative emotion expression groups based on the Courtauld Emotional Control Scale scores. The researchers compared POMS scores before and after biopsy results among the eight subgroups.

In women with breast cancer, the total mood disturbance scores were significantly higher among those in the high anxiety subgroup than in the low anxiety subgroup. Those scores were higher in the negative emotion suppression group than in the negative emotion expression group.

Among women with benign tumors, those in the high anxiety subgroup showed higher overall total mood disturbance scores at the first visit. The total mood disturbance scores in the negative emotion expression group were not significantly different between the first and second clinic visits, regardless of the diagnosis.

RISPERDAL

(**RISPERIDONE**) TABLETS/ORAL SOLUTION

RISPERDAL® M-TAB®

(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION OF WHICH THE FOLLOWING IS A BRIEF SUMMARY. INDICATIONS AND USAGE

ADICATIONS AND USAGE
INSPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

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CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product. WARNINGS

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WARNINGS

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Cerebrovascular adverse events, Including Stroke, in Elderly Patients With Dementia Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® has not been shown to be safe or reflective in the treatment of patients with dementia-related psychosis.

Hyperglycemia and Diabetes Mellitus Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with placebo. RISPERDAL® Patients with an established diagnosis of diabetes mellitus who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and perio

General Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-thration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or repeatic impairment (See DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihyportension were medication.

res: RISPERDAL® should be used cautiously in patients with a history of seizures.

Seizures: RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Osteodystrophy and Tumors in Animats: RISPERDAL® CONSTA^{N®} produced osteodystrophy in male and female rats in a 1-year toxicity study and a 2-year carcinogenicity study at a dose of 40 mg/kg administered IM every 2 weeks. RISPERDAL® CONSTA^{N®} produced renal tubular tumors (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. In addition, RISPERDAL® CONSTA^{N®} produced an increase in a marker of cellular proliferation in renal tissue in males in the 1-year toxicity study and in renal tumor-bearing males in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks.

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Hyperprolacimemia: As with other drugs that antagonize dopamine D, receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Polential for Cognitive and Motor Impaliment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy dose not affect them adversely.

Priapism: Rare cases of priapism have been reported.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Sulcide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients

Patients With Concomitant Interest in schizophrenia, and close supervision of high risk patients should accompany drug therapy.

West Patients With Concomitant Illness:** Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolisim or hemodynamic responses.

Because of the risks of orthostatic hypotension and CT prolongation, caution should be observed in cardiac patients (see WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment and in patients with severe hepatic impairment. A lower starting dose should be used in such patients.

A lower starting dose should be used in such patients. Information for Patients Physicians are advised to consult full prescribing information to review issues to be discussed with patients for whom they prescribe RISPERDAL®.

*Phenylketonurics** Phenylalanine is a component of aspartame. Each 2 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

pnenylalanine.

Drug Interactions: The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol. Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential. RISPERDAL® may antagonize the effects of levodopa and dopamine agonists. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

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Carbamazepine and Other Enzyme Inducers: In a drug interaction study in schizophrenic patients, 11 subjects received risperidone utilities of the patients of the patie

UTIONS, GENERAL).

No evidence of mutagenic potential for risperidone was found.

ent of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies at doses 0.1 to 3 times the recommended human dose on a mg/m² basis.

Impairment or resumpt, 1 support of the maximum recommended human dose on a mg/m² basis.

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose (MRHD) on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lacation at doses of 0.165 mg/kg or 0.1 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m² basis. In a cross-fostering study in Wistar

rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but rearred by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m² basis. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL® therapy is unknown. RISPERDAL® should be used during pregnancy The potential benefit justifies the potential risk to the feture. In exausal relationship to RISPERDAL® therapy is unknown. RISPERDAL® should be used during pronjy if the potential benefit justifies the potential risk to the feture. Labor and Delivery The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human bre. Therefore, women receiving isperidone should not breast-feed.

Pediatric Use Safety and effectiveness in children have not been established.

Nursing Mothers in animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Hisperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-fee.

Pediatric Use Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOSY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of comment. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

Concomitant use with Furosemide in Elderly Patients with Dementia in placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 89 years, range 70-97) when compared to patients treated with furosemide plus oral risperidone and some age 84 years, range 70-96 or furosemide alone (4

ADVERSE REACTIONS

ADVERSE REACTIONS
Associated With Discontinuation of Treatment
Biploral Mania in the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (71/25) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%).

In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo).

Incidence in Controlled Trials Commonly Observed Adverse Events in Controlled Clinical Trials:

Bipolar Mania: In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence in 4 lacet Mixel Pated of placebo).

Bipotar Mania: In the US placebo-controlled that with rispendone as monotherapy, the most commonly observed adverse events associated with the use of HISPEHDIA!* (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with rispendone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence. Adverse Events Occurring at an incidence of 2% or More Among RISPERDAL® Patients - Bipotar Mania Adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World

Adverse events that occurred at an incidence of 2% or more, and were more usequent among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial [Monotherapy in Bipolar Mania]

Body System/Preferred Term

Central & peripheral nervous system: Dystonia, Akathisia, Dizziness, Parkinsonism, Hypoaesthesia. Psychiatric: Somnolence, Agitation, Manic reaction, Anxiety, Concentration impaired Gastrointestinal system: Dyspepsia, Nausea, Saliva increased, Mouth dry. Body as a whole - general: Pain, Falique, Injuny. Respiratory system: Sinusitis, Rhintis, Coughing Skin and appendage: Acne, Pruntus Musculo-Skeletal: Myalgia, Skietela pain Metabolic and nutritional: Weight increase Vision disorders: Vision abnormal Cardiovascular, general: Hypetension, Hypotension, Heart rate and rhythm: Tachycardia Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial [Adjunctive Therapy in Bipolar Mania]

Body System/Preferred Term

Gastrointestinal system: Saliva increased, Diarrhea, Abdominal pain, Constipation, Mouth dry, Tooth ache, Tooth disorder *Central & peripheral nervous system: Dizziness, Parkinsonism, Akathisia, Dystonia *Psychiatric: Somnolence, Anxiety, Contision *Respiratory system: Phinitis, Pharyngilis, Coughing *Body as a whole - general: Asthenia *Urinary system: Uniary incontinence Heart rate and rhythm: Tachycardia *Metabolic and nutritional: Weight increase *Skin and appendages: Rash *Dose Dependency of Adverse Events:

Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment. These symptoms include: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dupotential vigential increased pigential symptoms associated with risperidone treatment. These symptoms include: sleepiness, increased duration of selep, accommodation disturbances

Laboratory Changes: A between group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL*/placebo differences in the proportions of patients experiencing opentally important changes in routine seerum chemistry, hematology, or urinalysis, parameters. Similarly, there were no RISPERDAL*/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis, however, RISPERDAL* administration was associated with increases in serum profactin (see PRECAUTIONS).

ECG Changes: Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including CT (CT, can PCR intervals, and heart rate. When all RISPERDAL* doses were pooled from randomized controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including CT (CT, can PCR intervals, and heart rate.) When all RISPERDAL* doses were pooled from randomized controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including CT (CT, can PCR intervals, and heart rate to Compared to placebo (4-6 beats per minute).

Other Events Observed During the Pre-Marketing Evaluation

During its premarketing assessment, multiple doses of RISPERDAL* (risperidone) were administered to 2607 patients in phase 2 and 3 studies and the following reactions were reported: (Note: "inequent adverse events are those occurring in 1100 to 111000 patients." Intervent increased steepers in foreased diverse events are those occurring in 1100 to 111000 patients. Intervent increased steepers and the second properties of the prop

psychotic patients whether they remain unrecases.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

A treatment of overdosage, see full prescribing information. For information on symptoms and treatment of overdosage, More detailed professional information is available upon request. © Janssen 2003

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