

Diabetics Differ by Gender in Depression Risk

BY BRUCE JANCIN

ISTANBUL — The risk of comorbid depression is particularly strong in relatively young people with type 2 diabetes, according to a nationwide Norwegian study.

In Norwegian men with type 2 diabetes, the risk of unipolar depressive disorder peaked when they were in their 20s, with a prevalence 3.54-fold greater

than in age-matched nondiabetic men, Dr. Line I. Berge reported at the annual congress of the European College of Neuropsychopharmacology.

In contrast, the prevalence of unipolar depression in Norwegian women with type 2 diabetes women peaked when they were in their 40s; the rate among similarly aged women without diabetes was 2.4-fold higher.

By the time Norwegian men with type

2 diabetes were in their 40s, their risk of depression was increased 2.35-fold, compared with age-matched controls, a considerable drop off from their peak rate when they were 2 decades younger, added Dr. Berge, a psychiatrist at the University of Bergen (Norway).

She presented an analysis of data for the year 2006 from the Norwegian Prescription Database, a comprehensive record of all physician-prescribed drugs

for appropriately diagnosed outpatients in the nation of 4.8 million people.

Depression and diabetes are two of the most common diseases in the Western world.

The prevalence of unipolar depressive disorder among Norwegian adults in 2006 was 5.3%, while the prevalence of type 2 diabetes was 1.6%.

The overall risk of comorbid unipolar depression in individuals with type 2

TOVIAZ® (fesoterodine fumarate) extended release tablets

Rx only

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

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

INDICATIONS AND USAGE

Toviaz is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

Toviaz is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Toviaz is also contraindicated in patients with known hypersensitivity to the drug or its ingredients.

PRECAUTIONS

General

Bladder Outlet Obstruction: Toviaz should be administered with caution to patients with clinically significant bladder outlet obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

Decreased Gastrointestinal Motility: Toviaz, like other antimuscarinic drugs, should be used with caution in patients with decreased gastrointestinal motility, such as those with severe constipation.

Controlled Narrow-Angle Glaucoma: Toviaz should be used with caution in patients being treated for narrow-angle glaucoma, and only where the potential benefits outweigh the risks (see **CONTRAINDICATIONS**).

Reduced Hepatic Function: There are no dosing adjustments for patients with mild or moderate hepatic impairment. Toviaz has not been studied in patients with severe hepatic impairment and therefore is not recommended for use in this patient population (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information and **DOSAGE AND ADMINISTRATION**).

Myasthenia Gravis: Toviaz should be used with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

Reduced Renal Function: There are no dosing adjustments for patients with mild or moderate renal insufficiency. Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal insufficiency (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information and **DOSAGE AND ADMINISTRATION**).

Concomitant Administration with CYP3A4 Inhibitors: Doses of Toviaz greater than 4 mg are not recommended in patients taking a potent CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, clarithromycin).

In patients taking weak or moderate CYP3A4 inhibitors (e.g. erythromycin), careful assessment of tolerability at the 4 mg daily dose is advised prior to increasing the daily dose to 8 mg. While this specific interaction potential was not examined by clinical study, some pharmacokinetic interaction is expected, albeit less than that observed with potent CYP3A4 inhibitors (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions** in full prescribing information and **DOSAGE AND ADMINISTRATION**).

Information for Patients

Patients should be informed that Toviaz, like other antimuscarinic agents, may produce clinically significant adverse effects related to antimuscarinic pharmacological activity including constipation and urinary retention. Toviaz, like other antimuscarinics, may be associated with blurred vision, therefore, patients should be advised to exercise caution until the drug's effects on the patient have been determined. Heat prostration (due to decreased sweating) can occur when Toviaz, like other antimuscarinic drugs, is used in a hot environment. Patients should also be informed that alcohol may enhance the drowsiness caused by Toviaz, like other anticholinergic agents. Patients should read the patient leaflet entitled "Patient Information TOVIAZ" before starting therapy with Toviaz.

Drug Interactions

Coadministration of Toviaz with other antimuscarinic agents that produce dry mouth, constipation, urinary retention, and other anticholinergic pharmacological effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. Also see **PRECAUTIONS, Concomitant Administration with CYP3A4 Inhibitors**.

Drug-Laboratory Test Interactions

Interactions between Toviaz and laboratory tests have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of drug-related carcinogenicity was found in 24-month studies with oral administration to mice and rats. The highest tolerated doses in mice (females 45 to 60 mg/kg/day, males 30 to 45 mg/kg/day) correspond to 11- to 19-fold (females) and 4- to 9-fold (males) the estimated human AUC values reached with fesoterodine 8 mg, which is the Maximum Recommended Human Dose (MRHD). In rats, the highest tolerated dose (45 to 60 mg/kg/day) corresponds to 3- to 8-fold (females) and 3- to 14-fold (males), the estimated human AUC at the MRHD.

Fesoterodine was not mutagenic or genotoxic in vitro (Ames tests, chromosome aberration tests) or in vivo (mouse micronucleus test).

Fesoterodine had no effect on reproductive function, fertility, or early embryonic development of the fetus at non-maternally toxic doses in mice. The maternal No-Observed-Effect Level (NOEL) and the NOEL for effects on reproduction and early embryonic development were both 15 mg/kg/day. Based on AUC, the systemic exposure was 0.6- to 1.5-fold higher in mice than in humans at the MRHD, whereas based on peak plasma concentrations, the exposure in mice was 5- to 9-fold higher. The Lowest-Observed-Effect Level (LOEL) for maternal toxicity was 45 mg/kg/day.

Pregnancy

Pregnancy Category C

Reproduction studies have been performed in mice and rabbits. No dose-related teratogenicity was observed at oral doses up to 75 mg/kg/day in mice (6 to 27 times the expected exposure at the MRHD based on AUC and greater than 77 times the expected C_{max}) and up to 27 mg/kg/day in rabbits (3- to 11-fold by AUC and 19- to 62-fold by C_{max}) or at subcutaneous doses up to 4.5 mg/kg/day in rabbits (9- to 11-fold by AUC and 43- to 56-fold by C_{max}). In mice treated orally with 75 mg/kg/day (6- to 27-times the expected exposure at the MRHD based on AUC and greater than 77-times the expected C_{max}), increased resorptions and decreased live fetuses were observed. One fetus with cleft palate was observed at each dose (15, 45 and 75 mg/kg/day), at an incidence within the background historical range. In rabbits treated orally with 27 mg/kg/day (3- to 11-fold by AUC and 19- to 62-fold by C_{max}), incompletely ossified sternbrae (retardation of bone development) were observed in fetuses. In rabbits treated by subcutaneous (sc) administration with 4.5 mg/kg/day (9- to 11-fold by AUC and 43- to 53-fold by C_{max}), maternal toxicity and incompletely ossified sternbrae were observed in fetuses (at an incidence within the background historical range). At 1.5 mg/kg/day s.c., (3-fold by AUC and 11- to 13-fold by C_{max}), decreased maternal food consumption in the absence of any fetal effects was observed. Oral administration of 30 mg/kg/day fesoterodine to mice in a pre- and post-natal development study resulted in decreased body weight of the dams and delayed ear opening of the pups. No effects were noted on mating and reproduction of the F_1 dams or on the F_2 offspring.

There are no adequate and well-controlled studies using Toviaz in pregnant women. Therefore, Toviaz should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers

It is not known whether fesoterodine is excreted in human milk. Toviaz should not be administered during nursing unless the potential benefit outweighs the potential risk to the neonate.

Pediatric Use

The safety and effectiveness of Toviaz in pediatric patients have not been established.

Geriatric Use

Of 1567 patients who received Toviaz 4 mg/day or 8 mg/day in the Phase 2 and 3, placebo-controlled, efficacy and safety studies, 515 (33%) were 65 years of age or older, and 140 (9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies; however, the incidence of antimuscarinic adverse events, including dry mouth, constipation, dyspepsia, increase in residual urine, dizziness (at 8 mg only) and urinary tract infection, was higher in patients 75 years of age and older as compared to younger patients (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** and **CLINICAL STUDIES** in full prescribing information and **ADVERSE REACTIONS**).

ADVERSE REACTIONS

The safety of Toviaz was evaluated in Phase 2 and 3 controlled trials in a total of 2859 patients with overactive bladder of which 2288 were treated with fesoterodine. Of this total, 782 received Toviaz 4 mg/day, and 785 received Toviaz 8 mg/day in Phase 2 or 3 studies with treatment periods of 8 or 12 weeks. Approximately 80% of these patients had >10 weeks exposure to Toviaz in these trials.

A total of 1964 patients participated in two 12-week, Phase 3 efficacy and safety studies and subsequent open-label extension studies. In these 2 studies combined, 554 patients received Toviaz 4 mg/day and 566 patients received Toviaz 8 mg/day.

In Phase 2 and 3 placebo-controlled trials combined, the incidences of serious adverse events in patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg were 1.9%, 3.5%, and 2.9%, respectively. All serious adverse events were judged to be not related or unlikely to be related to study medication by the investigator, except for four patients receiving Toviaz who reported one serious adverse event each: angina, chest pain, gastroenteritis, and QT prolongation on ECG.

The most commonly reported adverse event in patients treated with Toviaz was dry mouth. The incidence of dry mouth was higher in those taking 8 mg/day (35%) and in those taking 4 mg/day (19%), as compared to placebo (7%). Dry mouth led to discontinuation in 0.4%, 0.4%, and 0.8% of patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg, respectively. For those patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment.

The second most commonly reported adverse event was constipation. The incidence of constipation was 2% in those taking placebo, 4% in those taking 4 mg/day, and 6% in those taking 8 mg.

Table 3 lists adverse events, regardless of causality, that were reported in the combined Phase 3, randomized, placebo-controlled trials at an incidence greater than placebo and in 1% or more of patients treated with Toviaz 4 mg or 8 mg once daily for up to 12 weeks.

Table 3. Adverse events with an incidence exceeding the placebo rate and reported by ≥1% of patients from double-blind, placebo-controlled Phase 3 trials of 12 weeks' treatment duration

System organ class	Preferred term	Placebo N=554 %	Toviaz 4 mg/day N=554 %	Toviaz 8 mg/day N=566 %
Gastrointestinal disorders	Dry mouth	7.0	18.8	34.6
	Constipation	2.0	4.2	6.0
	Dyspepsia	0.5	1.6	2.3
	Nausea	1.3	0.7	1.9
	Abdominal pain upper	0.5	1.1	0.5
Infections	Urinary tract infection	3.1	3.2	4.2
	Upper respiratory tract infection	2.2	2.5	1.8
Eye disorders	Dry eyes	0	1.4	3.7
Renal and urinary disorders	Dysuria	0.7	1.3	1.6
	Urinary retention	0.2	1.1	1.4
Respiratory disorders	Cough	0.5	1.6	0.9
	Dry throat	0.4	0.9	2.3
General disorders	Edema peripheral	0.7	0.7	1.2
Musculoskeletal disorders	Back pain	0.4	2.0	0.9
Psychiatric disorders	Insomnia	0.5	1.3	0.4
Investigations	ALT increased	0.9	0.5	1.2
	GGT increased	0.4	0.4	1.2
Skin disorders	Rash	0.5	0.7	1.1

ALT=alanine aminotransferase, GGT=gamma glutamyltransferase

Patients also received Toviaz for up to three years in open-label extension phases of one Phase 2 and two Phase 3 controlled trials. In all open-label trials combined, 857, 701, 529, and 105 patients received Toviaz for at least 6 months, 1 year, 2 years, and 3 years respectively. The adverse events observed during long-term, open-label studies were similar to those observed in the 12-week, placebo-controlled studies, and included dry mouth, constipation, dry eyes, dyspepsia and abdominal pain. Similar to the controlled studies, most adverse events of dry mouth and constipation were mild to moderate in intensity. Serious adverse events, judged to be at least possibly related to study medication by the investigator, and reported more than once during the open-label treatment period of up to 3 years included urinary retention (3 cases), diverticulitis (3 cases), constipation (2 cases), irritable bowel syndrome (2 cases), and electrocardiogram QT corrected interval prolongation (2 cases).

OVERDOSAGE

Overdosage with Toviaz can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdosage, ECG monitoring is recommended.

DOSAGE AND ADMINISTRATION

The recommended starting dose of Toviaz is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily.

The daily dose of Toviaz should not exceed 4 mg in the following populations:

- Patients with severe renal insufficiency ($CL_{CR} < 30$ mL/min).
- Patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin.

Toviaz is not recommended for use in patients with severe hepatic impairment (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information and **PRECAUTIONS**).

Toviaz should be taken with liquid and swallowed whole. Toviaz can be administered with or without food, and should not be chewed, divided, or crushed.

Manufactured by:

SCHWARZ PHARMA PRODUKTIONS-GmbH, 08056 Zwickau, Germany

Distributed by: Pfizer Labs, Division of Pfizer Inc, NY, NY 10017

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Impaired Social Interaction Flags Autism Early

BOSTON — Social difficulty and repetitive behaviors are better early flags of autism than are communication problems, according to one family physician.

Lack of spontaneous sharing is an early indicator of autism, said Dr. David Gregory, an assistant professor of clinical family medicine at the University of Virginia in Lynchburg and director of pediatric education.

Children with an autism spectrum disorder tend not to volunteer information about what they are thinking, doing, or feeling, Dr. Gregory said. "They have a sense of self that separates them from others."

Autistic children often engage in repetitive, compulsive behaviors that can be difficult to distinguish from obsessive-compulsive disorder. If you see a 2-year-old who is engaging in repetitive behaviors frequently, it could be an early indicator of autism.

Repetitive behaviors are common in the normal toddler, but the autistic child's repetitive behavior will be focused on the parts, rather than the whole. For example, the autistic child will spend hours focused on the wheel of a truck but not seem to notice that the truck can move. Older autistic children tend to focus on more complex subjects, he said.

One tool that physicians can use is the joint attention screen. The test involves shaking keys or making another loud noise. Watch to see if the child looks to the source of the noise, then at their parents to "share" the experience, and back to the object.

It is a good sign if the child looks toward the object making the noise. However, the most important part of the test is for the child to look at the parent for acknowledgment and then focus back on the object together.

Shared attention is an important potential indicator of social impairment that can be observed in the office in a brief amount of time.

Dr. Gregory recommends using a joint attention screen at the 6- or 9-month well visit. If a child fails to demonstrate joint attention, consider an earlier evaluation of the child with a standardized autism screening test, he said.

—Mary Ellen Schneider

diabetes was 2.54-fold greater than in people without diabetes.

The explanation for the age- and gender-related differences in comorbidity is unclear.

The Norwegian data were not adjusted for known risk factors for type 2 diabetes, such as obesity, smoking, and sedentary behavior, but it's unlikely that those potential confounders would explain the disparate findings with regard to gender and age, she continued.

This study has the strength of including the entire Norwegian population, providing a large enough sample size to

look at age-related differences. The study's major limitation is that it is cross-sectional, making it impossible to say whether type 2 diabetes is a risk factor for depression or vice versa. But data from the U.S. longitudinal Multi-Ethnic Study of Atherosclerosis (MESA) suggest the relationship is bidirectional, Dr. Berge noted.

MESA prospectively followed more than 5,200 participants without baseline diabetes and showed that those with baseline depressive symptoms had a "modest" increase in new-onset type 2 diabetes during 3.2 years of follow-up,

even after adjustment for potential confounders.

Similarly, those with baseline type 2 diabetes had an increased rate of new-onset depressive symptoms during follow-up (JAMA 2008;299:2751-9).

The observed bidirectionality is biologically plausible in that depression involves neuroendocrine activation and a chronic inflammatory state that can induce insulin resistance, while the burden of managing type 2 diabetes causes psychological stress which might increase depressive symptoms.

It is particularly interesting to note

that study participants with impaired fasting glucose or untreated type 2 diabetes had a lower risk of developing depressive symptoms than did normoglycemic controls, according to the MESA investigators.

"These findings suggest that clinicians should be aware of the increased risk of depressive symptoms in individuals with treated type 2 diabetes and consider routine screening for depressive symptoms among these patients," concluded Dr. Sherita H. Golden of Johns Hopkins University, Baltimore, and her MESA coinvestigators. ■

Escitalopram Most Effective in Severe Disease

ISTANBUL — The more severe a patient's baseline depression, the greater the efficacy displayed by escitalopram in a large observational Greek study.

Escitalopram (Lexapro) also proved exceptionally well tolerated in this 3,931-patient, 186-site naturalistic study, with a mere 7.8% discontinuation rate for any reason, Dr. Vasiliki Lagari reported at the annual congress of the European College of Neuropsychopharmacology.

The mean duration of the current episode of major depression among study participants was 1.8 years. For 62%, this was their first episode of major depressive disorder, according to Dr. Lagari of the Tripolis (Greece) Psychiatric Hospital.

At enrollment in the open-label 3-month study, 16% of patients were classified as having mild depression based upon a Clinical Global Impression of Severity (CGI-S) score of 3 on the 7-point scale. Fifty-four percent had moderate depression as defined by a CGI-S score of 4, and 30% had severe depression. The mean baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score was 26.7.


The mean reduction in MADRS score from baseline through 3 months was 22.6 points in the group with severe depression. That was a significantly greater improvement than in the moderately depressed group, which had a mean 17.7-point improvement, and this, in turn, was a significantly greater reduction than the 13.5-point decrease in patients with mild depression.

The same pattern of greater improvement in patients with more severe depression was seen in terms of CGI-S scores. However, the remission rate as defined by a CGI-S score of 2 or less approached 90% in patients with mild depression at baseline, a rate more than twice that of the severely depressed group, Dr. Lagari continued.


One or more adverse events were reported by 6.5% of patients on escitalopram only. The rate was three-fold higher in those on concomitant therapy.

The study was funded by a grant from Lundbeck, the manufacturer of escitalopram.

—Bruce Jancin

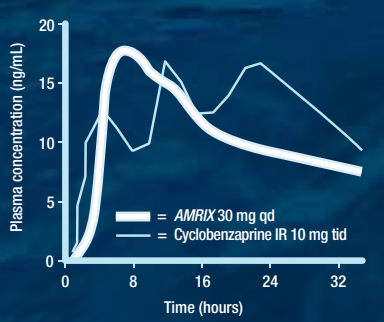


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AMRIX (Cyclobenzaprine Hydrochloride Extended-Release Capsules) is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle spasm and its associated signs and symptoms; namely, pain, tenderness, and limitation of motion. AMRIX should be used only for short periods (up to 2 or 3 weeks). AMRIX has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.


AMRIX is contraindicated in patients who are hypersensitive to any of its components. AMRIX is contraindicated with concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation. AMRIX may have life-threatening interactions with MAO inhibitors. AMRIX is contraindicated during the acute recovery phase of myocardial infarction; in patients with arrhythmias, heart block conduction disturbances, or congestive heart failure; or in patients with hyperthyroidism. AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants. AMRIX should not be used in elderly patients or in patients with impaired hepatic function. In clinical trials, the most commonly reported adverse reactions (≥3%) with AMRIX were dry mouth, dizziness, fatigue, nausea, dyspepsia, and constipation.

Please see brief summary of full prescribing information on the following page.

Reference: 1. Data on file. Study 1107. Cephalon, Inc.; 2004.

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