Dementia Rates to Rise 8% Over Next 20 Years

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London Bureau

People older than 95 are nearly 20 times as likely to die with dementia as those who die between the ages of 65 and 69, according to a population-based study in England and Wales.

The study demonstrates that the prevalence of dementia increases with age and that those who reach the age of 80 without mental impairment can still become demented as they continue to age, suggesting that with increasing life expectancy the number of people with dementia also will increase, the investigators reported. Based on the results of the study, the researchers estimated that the number of people who die each year with dementia is 114,000 in England and Wales and 487,000 in the United States; these numbers will increase in 20 years to 138,000 andd 528,000, respectively.

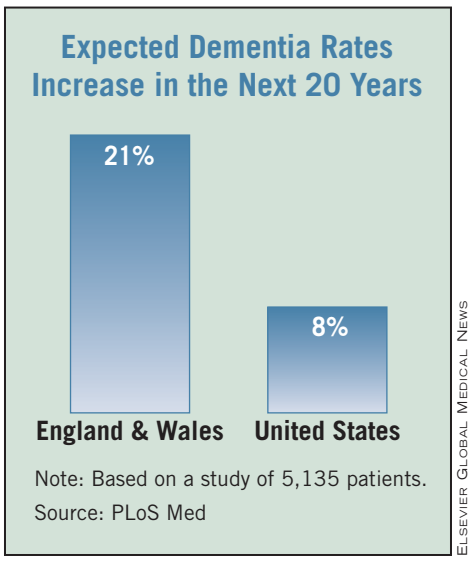
The investigators analyzed patients in the Medical Research Council Cognitive Function and Aging Study, which enrolled 13,004 patients at centers in Liverpool, Newcastle, Nottingham, Oxford, and Cambridgeshire in England and Gwynedd in north Wales (PLoS Med 2006 Oct. 31 [Epub doi10.1371/journal.pmed.0030397]).

The study followed 2,558 patients who were classified as having severe cognitive impairment and 2,577 who were classified as having moderate/severe cognitive impairment as measured by the Geriatric Mental State interview.

Of the 768 people who had died within 1 year of their last interview, 30% were suffering from dementia. Of those ages 65-69 years, just 6% had dementia, but of those age 95 years and older, 58% were suffering from dementia, according to the study.

Led by Dr. Carol Brayne, professor of public health medicine at University of Cambridge, the researchers wrote that the prevalence of dementia demonstrated in their study suggests that prevention may have a negligible effect in an aging society.

"It may be that, although there will be a preventable component to dementia giving us a small and important absolute reduction in expectation of dementia at given ages, there is also a component that is not amenable to such types of prevention," the authors said. "Researchers may be doing those who are aging now and themselves a disservice in the future if they assume, and project to the public, that dementia and cognitive impairment can be prevented altogether during increasingly long lives. ■



6%), anorexia (4% vs 2%), dysphagia (2% vs 0%). ***Metabolic and nutritional system:*** peripheral edema (5% vs 4%), decreased weight (2% vs 0%). ***Nervous system:*** dizziness (25% vs 24%), somnolence (22% vs 9%), insomnia (17% vs 12%), hallucinations (9% vs 3%), confusion (4% vs 1%), amnesia (4% vs 2%), hypesthesia (3% vs 1%), dystonia (2% vs 1%), akathisia (2% vs 0%), thinking abnormalities (2% vs 0%), decreased libido (1% vs 0%), myoclonus (1% vs 0%). ***Special senses:*** vision abnormalities (3% vs 0%). ***Urogenital system:*** impotence (2% vs 1%). Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients with early Parkinson's disease and treated with Mirapex® (pramipexole dihydrochloride) tablets but reported equally or more frequently in the placebo group were infection, accidental injury, headache, pain, tremor, back pain, syncope, postural hypotension, hypertonia, depression, abdominal pain, anxiety, dyspepsia, flatulence, diarrhea, rash, ataxia, dry mouth, extrapyramidal syndrome, leg cramps, twitching, pharyngitis, sinusitis, sweating, rhinitis, urinary tract infection, vasodilation, flu syndrome, increased saliva, tooth disease, dyspnea, increased cough, gait abnormalities, urinary frequency, vomiting, allergic reaction, hypertension, pruritus, hypokinesia, increased creatine PK, nervousness, dream abnormalities, chest pain, neck pain, paresthesia, tachycardia, vertigo, voice alteration, conjunctivitis, paralysis, accommodation abnormalities, tinnitus, diplopia, and taste perversions.

In a fixed-dose study in early Parkinson's disease, occurrence of the following events increased in frequency as the dose increased over the range from 1.5 mg/day to 6 mg/day: postural hypotension, nausea, constipation, somnolence, and amnesia. The frequency of these events was generally 2-fold greater than placebo for pramipexole doses greater than 3 mg/day. The incidence of somnolence with pramipexole at a dose of 1.5 mg/day was comparable to that reported for placebo.

Advanced Parkinson's Disease: In the four double-blind, placebo-controlled trials of patients with advanced Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX tablets and concomitant levodopa were postural (orthostatic) hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, and urinary frequency.

Approximately 12% of 260 patients with advanced Parkinson's disease who received Mirapex® (pramipexole dihydrochloride) tablets and concomitant levodopa in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 16% of 264 patients who received placebo and concomitant levodopa. The events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [2.7% on MIRAPEX tablets vs 0.4% on placebo]; dyskinesia [1.9% on MIRAPEX tablets vs 0.8% on placebo]; extrapyramidal syndrome [1.5% on MIRAPEX tablets vs 4.9% on placebo]; dizziness [1.2% on MIRAPEX tablets vs 1.5% on placebo]; confusion [1.2% on MIRAPEX tablets vs 2.3% on placebo]); and cardiovascular system (postural [orthostatic] hypotension [2.3% on MIRAPEX tablets vs 1.1% on placebo]).

Adverse-event Incidence in Controlled Clinical Studies in Advanced Parkinson's Disease: This section lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in advanced Parkinson's disease that were reported by 1% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group. In these studies, MIRAPEX tablets or placebo was administered to patients who were also receiving concomitant levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Treatment-emergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=260) vs placebo (N=264), respectively. ***Body as a whole:*** accidental injury (17% vs 15%), asthenia (10% vs 8%), general edema (4% vs 3%), chest pain (3% vs 2%), malaise (3% vs 2%). ***Cardiovascular system:*** postural hypotension (53% vs 48%). ***Digestive system:*** constipation (10% vs 9%), dry mouth (7% vs 3%). ***Metabolic and nutritional system:*** peripheral edema (2% vs 1%), increased creatine PK (1% vs 0%). ***Musculoskeletal system:*** arthritis (3% vs 1%), twitching (2% vs 0%), bursitis (2% vs 0%), myasthenia (1% vs 0%). ***Nervous system:*** dyskinesia (47% vs 31%), extrapyramidal syndrome (28% vs 26%), insomnia (27% vs 22%), dizziness (26% vs 25%), hallucinations (17% vs 4%), dream abnormalities (11% vs 10%), confusion (10% vs 7%), somnolence (9% vs 6%), dystonia (8% vs 7%), gait abnormalities (7% vs 5%), hypertonia (7% vs 6%), amnesia (6% vs 4%), akathisia (3% vs 2%), thinking abnormalities (3% vs 2%), paranoid reaction (2% vs 0%), delusions (1% vs 0%), sleep disorders (1% vs 0%). ***Respiratory system:*** dyspnea (4% vs 3%), rhinitis (3% vs 1%), pneumonia (2% vs 0%). ***Skin and appendages:*** skin disorders (2% vs 1%). ***Special senses:*** accommodation abnormalities (4% vs 2%), vision abnormalities (3% vs 1%), diplopia (1% vs 0%). ***Urogenital system:*** urinary frequency (6% vs 3%), urinary tract infection (4% vs 3%), urinary incontinence (2% vs 1%). Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients with advanced Parkinson's disease and treated with Mirapex® (pramipexole dihydrochloride) tablets but reported equally or more frequently in the placebo group were nausea, pain, infection, headache, depression, tremor, hypokinesia, anorexia, back pain, dyspepsia, flatulence, ataxia, flu syndrome, sinusitis, diarrhea, myalgia, abdominal pain, anxiety, rash, paresthesia, hypertension, increased saliva, tooth disorder, apathy, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hypesthesia, neck pain, syncope, arthralgia, dysphagia, palpitations, pharyngitis, vertigo, leg cramps, conjunctivitis, and lacrimation disorders.

Restless Legs Syndrome: MIRAPEX tablets for treatment of RLS have been evaluated for safety in 889 patients, including 427 treated for over six months and 75 for over one year.

The overall safety assessment focuses on the results of three double-blind, placebo-controlled trials, in which 575 patients with RLS were treated with MIRAPEX tablets for up to 12 weeks. The most commonly observed adverse events with MIRAPEX tablets in the treatment of RLS (observed in >5% of pramipexole-treated patients and at a rate at least twice that observed in placebo-treated patients) were nausea and somnolence. Occurrences of nausea and somnolence in clinical trials were generally mild and transient.

Approximately 7% of 575 patients treated with MIRAPEX tablets during the double-blind periods of three placebo-controlled trials discontinued treatment due to adverse events compared to 5% of 223 patients who received placebo. The adverse event most commonly causing discontinuation of treatment was nausea (1%).

This section lists treatment-emergent events that occurred in three double-blind, placebo-controlled studies in RLS patients that were reported by 2% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Treatment-emergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=575) vs placebo (N=223), respectively. ***Gastrointestinal disorders:*** nausea (16% vs 5%), constipation (4% vs 1%), diarrhea (3% vs 1%), dry mouth (3% vs 1%). ***General disorders and administration site conditions:*** fatigue (9% vs 7%). ***Infections and infestations:*** influenza (3% vs 1%). ***Nervous system disorders:*** headache (16% vs 15%), somnolence (6% vs 3%). Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

This section summarizes data for adverse events that appeared to be dose related in the 12-week fixed dose study. Dose related adverse events in a 12-week, double-blind, placebo-controlled, fixed dose study in Restless Legs Syndrome (occurring in 5% or more of all patients in the treatment phase) are listed by body system in order of decreasing incidence for MIRAPEX (0.25 mg [N=88]; 0.5 mg [N=80]; 0.75 mg [N=90]) vs placebo (n=86), respectively. ***Gastrointestinal disorders:*** nausea (11%; 19%; 27% vs 5%), diarrhea (3%; 1%; 7% vs 0%), dyspepsia (3%; 1%; 4% vs 7%). ***Infections and infestations:*** influenza (1%; 4%; 7% vs 1%). ***General disorders and administration site conditions:*** fatigue (3%; 5%; 7% vs 5%). ***Psychiatric disorders:*** insomnia (9%; 9%; 13% vs 9%), abnormal dreams (2%; 1%; 8% vs 2%). ***Respiratory, thoracic and mediastinal disorders:*** nasal congestion (0%; 3%; 6% vs 1%). ***Musculoskeletal and connective tissue disorders:*** pain in extremity (3%; 3%; 7% vs 1%).

Other events reported by 2% or more of RLS patients treated with Mirapex® (pramipexole dihydrochloride) tablets but equally or more frequently in the placebo group, were: vomiting, nasopharyngitis, back pain, pain in extremity, dizziness, and insomnia.

General

Adverse Events; Relationship to Age, Gender, and Race: Among the treatment-emergent adverse events in patients treated with MIRAPEX tablets, hallucination appeared to exhibit a positive relationship to age in patients with Parkinson's disease. Although no gender-related differences were observed in Parkinson's disease patients, nausea and fatigue, both generally transient, were more frequently reported by female than male RLS patients. Less than 4% of patients enrolled were non-Caucasian, therefore, an evaluation of adverse events related to race is not possible.

Other Adverse Events Observed During Phase 2 and 3 Clinical Trials: MIRAPEX tablets have been administered to 1620 Parkinson's disease patients and to 889 RLS patients in Phase 2 and 3 clinical trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing; similar types of events were grouped into a smaller number of standardized categories using MedDRA dictionary terminology. These categories are used in the listing below. Adverse events which are not listed above but occurred on at least two occasions (one occasion if the event was serious) in the 2509 individuals exposed to MIRAPEX tablets are listed below. The reported events below are included without regard to determination of a causal relationship to MIRAPEX tablets.

Blood and lymphatic system disorders: anemia, iron deficiency anemia, leukocytosis, leukopenia, lymphadenitis, lymphadenopathy, thrombocythaemia, thrombocytopenia. *Cardiac disorders:* angina pectoris, arrhythmia supraventricular, atrial fibrillation, atrioventricular block first degree, atrioventricular block second degree, bradycardia, bundle branch block, cardiac arrest, cardiac failure, cardiac failure congestive, cardiomegaly, coronary artery occlusion, cyanosis, extrasystoles, left ventricular failure, myocardial infarction, nodal arrhythmia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia, ventricular fibrillation, ventricular extrasystoles, ventricular hypertrophy. *Congenital, familial and genetic disorders:* atrial septal defect, congenital foot malformation, spine malformation. *Ear and labyrinth disorders:* deafness, ear pain, hearing impaired, hypoacusis, motion sickness, vestibular ataxia. *Endocrine disorders:* goiter, hyperthyroidism, hypothyroidism. *Eye disorders:* amaurosis fugax, blepharitis, blepharospasm, cataract, dacryostenosis acquired, dry eye, eye hemorrhage, eye irritation, eye pain, eyelid edema, eyelid ptosis, glaucoma, keratitis, macular degeneration, myopia, photophobia, retinal detachment, retinal vascular disorder, scotoma, vision blurred, visual acuity reduced, vitreous floaters. *Gastrointestinal disorders:* abdominal discomfort, abdominal distension, aphthous stomatitis, ascites, cheilitis, colitis, colitis ulcerative, duodenal ulcer, duodenal ulcer hemorrhage, enteritis, eructation, fecal incontinence, gastric ulcer, gastric ulcer hemorrhage, gastritis, gastrointestinal hemorrhage, gastroesophageal reflux disease, gingivitis, haematemesis, haematochezia, hemorrhoids, hiatus hernia, hyperchlorhydria, ileus, inguinal hernia, intestinal obstruction, irritable bowel syndrome, esophageal spasm, esophageal stenosis, esophagitis, pancreatitis, periodontitis, rectal hemorrhage, reflux esophagitis, tongue edema, tongue ulceration, toothache, umbilical hernia. *General disorders:* chest discomfort, chills, death, drug withdrawal syndrome, face edema, feeling cold, feeling hot, feeling jittery, gait disturbance, impaired healing, influenza-like illness, irritability, localized edema, edema, pitting edema, thirst. *Hepatobiliary disorders:* biliary colic, cholecystitis, cholecystitis chronic, cholelithiasis. *Immune system disorders:* drug hypersensitivity. *Infections and infestations:* abscess, acute tonsillitis, appendicitis, bronchiolitis, bronchitis, bronchopneumonia, cellulitis, cystitis, dental caries, diverticulitis, ear infection, eye infection, folliculitis, fungal infection, furuncle, gangrene, gastroenteritis, gingival infection, herpes simplex, herpes zoster, hordeolum, intervertebral discitis, laryngitis, lobar pneumonia, nail infection, onychomycosis, oral candidiasis, orchitis, osteomyelitis, otitis externa, otitis media, paronychia, pyelonephritis, pyoderma, sepsis, skin infection, tonsillitis, tooth abscess, tooth infection, upper respiratory tract infection, urethritis, vaginal candidiasis, vaginal infection, viral infection, wound infection. *Injury, poisoning and procedural complications:* accidental falls, drug toxicity epicondylitis, road traffic accident, sunburn, tendon rupture. *Metabolism and nutrition disorders:* cachexia, decreased appetite, dehydration, diabetes mellitus, fluid retention, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, hypovitaminosis, increased appetite, metabolic alkalosis. *Musculoskeletal and connective tissue disorders:* bone pain, fasciitis, flank pain, intervertebral disc disorder, intervertebral disc protrusion, joint effusion, joint stiffness, joint swelling, monarthritis, muscle rigidity, muscle spasms, musculoskeletal stiffness, myopathy, myositis, nuchal rigidity, osteoarthritis, osteonecrosis, osteoporosis, polymyalgia, rheumatoid arthritis, shoulder pain, spinal osteoarthritis, tendonitis, tenosynovitis. *Neoplasms benign, malignant and unspecified:* abdominal neoplasm, adenocarcinoma, adenoma benign, basal cell carcinoma, bladder cancer, breast cancer, breast neoplasm, chronic lymphocytic leukemia, colon cancer, colorectal cancer, endometrial cancer, gallbladder cancer, gastric cancer, gastrointestinal neoplasm, hemangioma, hepatic neoplasm, hepatic neoplasm malignant, lip and/or oral cavity cancer, lung neoplasm malignant, lung cancer metastatic, lymphoma, malignant melanoma, melanocytic naevus, metastases to lung, multiple myeloma, oral neoplasm benign, neoplasm, neoplasm malignant, neoplasm prostate, neoplasm skin, neuroma, ovarian cancer, prostate cancer, prostatic adenoma, pseudo lymphoma, renal neoplasm, skin cancer, skin papilloma, squamous cell carcinoma, thyroid neoplasm, uterine leiomyoma. *Nervous system disorders:* ageusia, akinesia, anticholinergic syndrome, aphasia, balance disorder, brain edema, carotid artery occlusion, carpal tunnel syndrome, cerebral artery embolism, cerebral hemorrhage, cerebral infarction, cerebral ischemia, chorea, cognitive disorder, coma, convulsion, coordination abnormal, dementia, depressed level of consciousness, disturbance in attention, dizziness postural, dysarthria, dysgraphia, facial palsy, grand mal convulsion, hemiplegia, hyperaesthesia, hyperkinesia, hyperreflexia, hyporeflexia, hypotonia, lethargy, loss of consciousness, memory impairment, migraine, muscle contractions involuntary, narcolepsy, neuralgia, neuropathy, nystagmus, parosmia, psychomotor hyperactivity, sciatica, sedation, sensory disturbance, sleep phase rhythm disturbance, sleep talking, stupor, syncope vasovagal, tension headache. *Psychiatric disorders:* affect lability, aggression, agitation, bradyphrenia, bruxism, suicide, delirium, delusional disorder persecutory type, disorientation, dissociation, emotional distress, euphoric mood, hallucination auditory, hallucination visual, initial insomnia, libido increased, mania, middle insomnia, mood altered, nightmare, obsessive thoughts, obsessive-compulsive disorder, panic reaction, parasomnia, personality disorder, psychotic disorder, restlessness, sleep walking, suicidal ideation. *Renal and urinary disorders:* chromaturia, dysuria, glycosuria, hematuria, urgency, nephrolithiasis, neurogenic bladder, nocturia, oliguria, pollakiuria, proteinuria, renal artery stenosis, renal colic, renal cyst, renal failure, renal impairment, urinary retention. *Reproductive system and breast disorders:* amenorrhea, breast pain, dysmenorrhea, epididymitis, gynaecomastia, menopausal symptoms, menorrhagia, metrorrhagia, ovarian cyst, priapism, prostatitis, sexual dysfunction, uterine hemorrhage, vaginal discharge, vaginal hemorrhage. *Respiratory, thoracic and mediastinal disorders:* apnea, aspiration, asthma, choking, chronic obstructive pulmonary disease, dry throat, dysphonia, dyspnea exertional, epistaxis, haemoptysis, hiccups, hyperventilation, increased bronchial secretion, laryngospasm, nasal dryness, nasal polyps, obstructive airways disorder, pharyngolaryngeal pain, pleurisy, pneumonia aspiration, pneumothorax, postnasal drip, productive cough, pulmonary embolism, pulmonary edema, respiratory alkalosis, respiratory distress, respiratory failure, respiratory tract congestion, rhinitis allergic, rhinorrhea, sinus congestion, sleep apnoea syndrome, sneezing, snoring, tachypnea, wheezing. *Skin and subcutaneous tissue disorders:* acne, alopecia, cold sweat, dermal cyst, dermatitis, dermatitis bullous, dermatitis contact, dry skin, ecchymosis, eczema, erythema, hyperkeratosis, livedo reticularis, night sweats, periorbital edema, petechiae, photosensitivity allergic reaction, psoriasis, purpura, rash erythematous, rash maculo-papular, rash papular, rosacea, seborrhea, seborrheic dermatitis, skin burning sensation, skin discoloration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, skin irritation, skin nodule, skin odor abnormal, skin ulcer, urticaria. *Vascular disorders:* aneurysm, angiopathy, arteriosclerosis, circulatory collapse, deep vein thrombosis, embolism, hematoma, hot flush, hypertensive crisis, lymphoedema, pallor, phlebitis, Raynaud's phenomenon, shock, thrombophlebitis, thrombosis, varicose vein.

Falling Asleep During Activities of Daily Living: Patients treated with Mirapex® (pramipexole dihydrochloride) tablets have reported falling asleep while engaged in activities of daily living, including operation of a motor vehicle which sometimes resulted in accidents (see bolded **WARNING**).

Post-Marketing Experience: In addition to the adverse events reported during clinical trials, the following adverse reactions have been identified during post-approval use of MIRAPEX tablets, primarily in Parkinson's disease patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to pramipexole tablets. Similar types of events were grouped into a smaller number of standardized categories using the MedDRA dictionary: abnormal behavior, abnormal dreams, accidents (including fall), blackouts, fatigue, hallucinations (all kinds), headache, hypotension (including postural hypotension), increased eating (including binge eating, compulsive eating, and hyperphagia), libido disorders (including increased and decreased libido, and hypersexuality), pathological gambling, syncope, and weight increase.

DRUG ABUSE AND DEPENDENCE

Pramipexole is not a controlled substance. Pramipexole has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, in a rat model on cocaine self-administration, pramipexole had little or no effect.

OVERDOSAGE

There is no clinical experience with massive overdosage. One patient, with a 10-year history of schizophrenia, took 11 mg/day of pramipexole for 2 days in a clinical trial to evaluate the effect of pramipexole in schizophrenic patients. No adverse events were reported related to the increased dose. Blood pressure remained stable although pulse rate increased to between 100 and 120 beats/minute. The patient withdrew from the study at the end of week 2 due to lack of efficacy.

There is no known antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdosage has not been assessed. Management of overdose may require general supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring.

ANIMAL TOXICOLOGY

Retinal Pathology in Albino Rats: Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study with pramipexole. These findings were first observed during week 76 and were dose dependent in animals receiving 2 or 8 mg/kg/day (plasma AUCs equal to 2.5 and 12.5 times the AUC in humans that received 1.5 mg TID). In a similar study of pigmented rats with 2 years' exposure to pramipexole at 2 or 8 mg/kg/day, retinal degeneration was not diagnosed. Animals given drug had thinning in the outer nuclear layer of the retina that was only slightly greater than that seen in control rats utilizing morphometry.

Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, degeneration and loss of photoreceptor cells occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (54 times the highest clinical dose on a mg/m^2 basis) and constant light (100 lux) but not in pigmented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats is considered to be uniquely sensitive to the damaging effects of pramipexole and light. Similar changes in the retina did not occur in a 2-year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.3, 2.2 and 11 times the highest clinical dose on a mg/m^2 basis). Evaluation of the retinas of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.4, 2.2, and 8.6 times the highest clinical dose on a mg/m^2 basis) for 12 months and minipigs given 0.3, 1, or 5 mg/kg/day of pramipexole for 13 weeks also detected no changes.

The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved.

Fibro-osseous Proliferative Lesions in Mice: An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0, or 10 mg/kg/day (0.3, 2.2, and 11 times the highest clinical dose on a mg/m^2 basis). Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The significance of this lesion to humans is not known.

Oxcarbazepine Found to Reduce AD Hypersexuality

MADRID — Oxcarbazepine appears to significantly decrease hypersexual behavior in patients with Alzheimer's disease, Dr. Joshua Shua-Haim reported in a poster at the 10th International Conference on Alzheimer's Disease and Related Disorders.

All 11 men in the small pilot study showed improvement in the behavior by 2 weeks of treatment, said Dr. Shua-Haim of the Jersey Shore University Medical Center, Neptune, N.J.

All of the patients lived in a special care unit in an assisted living facility. Treatment began with 150 mg oxcarbazepine daily. The dose was titrated by 150 mg/day, given in two divided doses, until the behavior ceased or a maximum of 900 mg/day was reached.

Hypersexual behavior resolved in all 11 patients, at an average dose of 600-750 mg/day, given in two doses. No adverse events were reported, and there were no changes in blood chemistry.

—Michele G. Sullivan