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Axillary Hyperhidrosis Shown Responsive to Botox

BY NANCY WALSH
New York Bureau

WASHINGTON — Botulinum toxin type A is a safe, effective treatment for bilateral, primary, axillary hyperhidrosis, according to the results of a randomized, double-blind study.

Sweat production was reduced by an average of more than 80% within 1 week of treatment, resulting in a high level of patient satisfaction, Dr. M.K. Naumann reported in a poster session at the annual meeting of the American Academy of Dermatology.

The study included 320 patients from several different European medical centers, 242 of whom received 10-15 injections of Botox (botulinum toxin type A) totalling 50 U in a concentration of 25 U/mL in each axilla.

The remaining 78 patients served as controls and received placebo injections.

After 4 weeks of treatment, 93.8% of subjects receiving the active treatment were considered responders, because they had a greater than 50% reduction in sweat production from baseline. By comparison, 35.9% of those in the placebo group evidenced the same level of reduction in sweat production.

The mean percentage reduction in sweat production at week 4 was 83.5% in the Botox group and 20.8% in the placebo group.

Treatment response persisted throughout the 16 weeks of the study in more than 80% of patients receiving Botox injections, "suggesting that a clinically significant reduction in sweating may persist well beyond the duration of the study period," said Dr. Naumann of the department of neurology, Bayerische Julius Maximilians Universitat Würzburg (Germany).

Adverse events in the active treatment group included increased nonaxillary sweating (4.5%), pruritus (0.8%), injection site pain (1.7%), pain (1.7%), and vasodilation (1.2%). None of the patients receiving placebo injections reported experiencing these adverse effects.

The treatment had no detectable effect on the production of neutralizing botulinum type A antibodies.

The study was sponsored by Allergan Inc., the manufacturer of Botox. The company is now completing phase III trials evaluating the drug for hyperhidrosis, and a new drug application is expected to be filed soon with the Food and Drug Administration. ■

ACCUTANE® (isotretinoin) CAPSULES

Before prescribing, please see complete product information, a summary of which follows:

CONTRAINDICATIONS AND WARNINGS: Accutane must not be used by females who are pregnant or who may become pregnant while undergoing treatment. Although not every fetus exposed to Accutane has resulted in a deformed child, there is an extremely high risk that a deformed infant can result if pregnancy occurs while taking Accutane in any amount even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. Presently, there are no accurate means of determining after Accutane exposure which fetus has been affected and which fetus has not been affected. Accutane is contraindicated in females of childbearing potential unless the patient meets all of the following conditions:

• must have severe disfiguring nodular acne that is recalcitrant to standard therapies (see INDICATIONS AND USAGE section for definition)
• must be reliable in understanding and carrying out instructions
• must be capable of complying with the mandatory contraceptive measures required for Accutane therapy and understand behaviors associated with an increased risk of pregnancy
• must have received both oral and written warnings of the hazards of taking Accutane during pregnancy and exposing a fetus to the drug
• must have received both oral and written information on the types of contraceptive methods and warnings about the rates of possible contraceptive failure, and of the need to use two separate, effective forms of contraception simultaneously, unless abstinence is the chosen method, or the patient has undergone a hysterectomy and has acknowledged in writing her understanding of the information and warnings and of the need for using two contraceptive methods simultaneously
• must have had a negative urine or serum pregnancy test with a sensitivity of at least 50 mIU/mL when the patient is qualified for Accutane therapy by the prescriber, and must have had a second negative urine or serum pregnancy test on the second day of the next normal menstrual period or at least 11 days after the last unprotected act of sexual intercourse, whichever is later
• must understand and agree that her prescriber will issue her a prescription for Accutane only after she has had negative results for two pregnancy tests as described above
• must have received instruction to join the Accutane Survey and have watched a videotape, provided by Roche to her prescriber, that provides information about contraceptive methods, possible reasons for contraceptive failure, and importance of using effective contraception when taking teratogenic drugs.
Major human fetal abnormalities related to Accutane administration have been documented: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); skull abnormality; external ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); cardiovascular abnormalities; facial dysmorphia; cleft palate; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted. Cases of IQ scores less than 85 with or without obvious CNS abnormalities have also been reported. There is an increased risk of spontaneous abortion. In addition, premature births have been reported. It is strongly recommended that a prescription for Accutane should not be issued by the prescriber until a female patient has had negative results from two urine or serum pregnancy tests, as described above. It is also recommended that pregnancy testing and counseling about contraception and behaviors associated with an increased risk of pregnancy be repeated monthly. In addition, the prescriber should prescribe no more than a 1-month supply of the drug for all Accutane patients and no automatic refills should be permitted; each time she will supply a female Accutane patients for the initial, secondary, and monthly testing during therapy. Effective contraception must be used for at least 1 month before beginning Accutane therapy, during therapy, and for 1 month following discontinuation of therapy even where there has been a history of infertility, unless due to hysterectomy. The patient must be counseled about and understand the limitations of any chosen contraceptive method. The patient must also understand the risks associated with using two contraceptive methods, even when one of the chosen methods is a hormonal contraceptive method. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use two effective forms of contraception simultaneously, unless absolute abstinence is the chosen method, even when one of the forms is a hormonal contraceptive method. Although hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as injectable/implantable contraceptive products. These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Accutane. If a pregnancy does occur during treatment, the prescriber and patient should discuss the desirability of continuing the pregnancy. Prescribers are encouraged to report all cases of pregnancy with specific information about the contraceptive forms used during Accutane therapy and for 1 month following therapy, either to the Roche Medical Services @ 1-800-526-5367 or to the Food and Drug Administration MedWatch Program @ 1-800-FDA-1088. Accutane should be prescribed only by prescribers who have special competence in the diagnosis and treatment of severe recalcitrant nodular acne, are experienced in the use of systemic retinoids, and understand the risk of teratogenicity if Accutane is used during pregnancy. Prescribers who prescribe Accutane should use the Pregnancy Prevention Program™ kit provided by Roche for the counseling of patients, should instruct the patient to participate in the Accutane Survey, and should recommend medical education sponsored by Roche about effective contraception, the limitations of contraceptive methods and behaviors associated with an increased risk of contraceptive failure and pregnancy.

INDICATIONS AND USAGE: Indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition, means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, Accutane should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, for female patients of childbearing potential, Accutane is indicated only for those females who are not pregnant (see boxed **CONTRAINDICATIONS AND WARNINGS**). **CONTRAINDICATIONS: Pregnancy: Category X. See boxed CONTRAINDICATIONS AND WARNINGS.** *Allergic Reactions:* Contraindicated in patients who are hypersensitive to this medication or to any of its components. Should not be given to patients who are sensitive to parabens (see PRECAUTIONS). **WARNINGS:** *Psychiatric Disorders:* **Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events (see ADVERSE REACTIONS:** *Psychiatric*). *Pseudotumor Cerebri:* **Accutane use has been associated with a number of cases of** pseudotumor cerebri (benign intracranial hypertension), **some of which involved concomitant use of tetracyclines. Concomitant treatment with tetracyclines should therefore be avoided. Early signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, they should be told to discontinue Accutane immediately and be referred to a neurologist for further diagnosis and care (see ADVERSE REACTIONS).** *Pancreatitis:* **Acute pancreatitis has been reported in patients with either elevated or normal serum triglyceride levels. In rare instances, fatal hemorrhagic pancreatitis has been reported.** Accutane should be stopped if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur. *Lipids:* Elevations of serum triglycerides have been reported. Marked elevations of serum triglycerides in excess of 800 mg/dL were reported in approximately 25% of patients receiving Accutane in clinical trials; approximately 15% developed a decrease in high-density lipoproteins and about 7% showed an increase in cholesterol levels. In clinical trials, the effects on triglycerides, HDL, and cholesterol were reversible upon cessation of therapy. Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in dose while continuing Accutane. Blood lipid determinations should be performed before Accutane is given and then at intervals until the lipid response is established, usually within 4 weeks. Especially careful consideration must be given to patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder. If Accutane therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended (see PRECAUTIONS). The cardiovascular consequences of hypertriglyceridemia associated with Accutane are unknown. *Animal Studies:* In rats given 8 or 32 mg/kg/day of isotretinoin for 18 months or longer, the incidences of focal calcification, fibrosis and inflammation of the myocardium, calcification of coronary, pulmonary and mesenteric arteries, and metastatic calcification of the gastric mucosa were greater than in control rats of similar age. Focal endocardial and myocardial calcifications associated with calcification of the coronary arteries were observed in two dogs after approximately 6 to 7 months of treatment with isotretinoin at a dosage of 60 to 120 mg/kg/day. *Hearing Impairment:* Impaired hearing has been reported in patients taking Accutane; in some cases, the hearing impairment has been reported to persist after therapy has been discontinued. Mechanism(s) and causality for this event have not been established. Patients who experience persistent tinnitus or hearing impairment should discontinue treatment and be referred to specialized care for further evaluation (see ADVERSE REACTIONS). *Hepatotoxicity:* Clinical hepatitis considered to be possibly or probably related to therapy has been reported. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials, some of which normalized with dosage reduction or continued administration of the drug. If normalization does not readily occur or if hepatitis is suspected during treatment, the drug should be discontinued and the etiology further investigated. *Inflammatory Bowel Disease:* Accutane has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. In some instances, symptoms have been reported to persist after treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue Accutane immediately (see ADVERSE REACTIONS). *Skeletal: Hyperostosis:* A high prevalence of skeletal hyperostosis was noted in clinical trials for disorders of keratinization with a mean dose of 2.24 mg/kg/day. Additionally, skeletal hyperostosis was noted in 6 of 8 patients in a prospective study of disorders of keratinization. Minimal skeletal hyperostosis and calcification of ligaments and tendons have also been observed by x-ray in prospective studies of nodular acne patients treated with a single course of therapy at recommended doses. The skeletal effects of multiple Accutane treatment courses for acne are unknown. *Premature Epiphyseal Closure:* There are spontaneous reports of premature epiphyseal closure in acne patients

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receiving recommended doses, but it is not known if there is a causal relationship with Accutane. In clinical trials for disorders of keratinization with a mean dose of 2.24 mg/kg/day, two children showed x-ray findings suggestive of premature epiphyseal closure. The skeletal effects of multiple Accutane treatment courses for acne are unknown. **Vision Impairment:** Visual problems should be carefully monitored. All patients experiencing visual difficulties should discontinue Accutane treatment and have an ophthalmological examination. *Corneal Opacities:* Corneal opacities have occurred in patients receiving Accutane for acne and more frequently when higher drug dosages were used in patients with disorders of keratinization. The corneal opacities that have been observed in clinical trial patients have either completely resolved or were resolving at follow-up 6 to 7 weeks after discontinuation of the drug (see ADVERSE REACTIONS). *Decreased Night Vision:* Decreased night vision has been reported during therapy and in some instances has persisted after therapy was discontinued. Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. **PRECAUTIONS:** *Information for Patients and Prescribers:* **Females of childbearing potential should be instructed that they must not be pregnant when therapy is initiated, and that they should use effective contraception while taking Accutane and for 1 month after Accutane has been stopped. They should also sign a consent form prior to beginning Accutane therapy. They should be instructed to join the Accutane Survey and to review the patient videotape provided by Roche to the prescriber that provides information about contraception, the most common reasons that contraception fails, and the importance of using effective contraception when taking teratogenic drugs. Female patients should also be seen monthly and have a urine or serum pregnancy test performed each month during treatment to confirm negative pregnancy status (see boxed CONTRAINDICATIONS AND WARNINGS).** Patients must not share Accutane with anyone else because of the risk of birth defects and other serious adverse events. Patients should not donate blood during therapy and for 1 month following discontinuance of the drug because the blood might be given to a pregnant woman whose fetus must not be exposed to Accutane. Transient exacerbation (flare) of acne has been seen, generally during the initial period of therapy. Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during therapy and for at least 6 months thereafter due to the possibility of scarring (see ADVERSE REACTIONS). Patients should avoid prolonged exposure to UV rays or sunlight. Patients may experience decreased tolerance to contact lenses during and after therapy. Approximately 16% of patients treated with Accutane in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of the drug. Transient pain in the chest has been reported less frequently. In a clinical trial, these symptoms generally cleared rapidly after discontinuation of Accutane, but in some cases persisted. Neutropenia and rare cases of agranulocytosis have been reported. Accutane should be discontinued if clinically significant decreases in white cell counts occur. *Hypersensitivity:* Anaphylactic reactions and other allergic reactions have been reported. Cutaneous allergic reactions and serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement (including renal) have been reported. Severe allergic reaction may necessitate interruption of therapy and appropriate medical management. *Drug Interactions:* Because of the relationship of Accutane to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects. Concomitant treatment with Accutane and tetracyclines should be avoided. Microdosed progesterone preparations (minipills) may be an inadequate method of contraception during therapy. It is not known if other hormonal contraceptive drugs differ in their effectiveness when used with Accutane. *Laboratory Tests: Pregnancy Test:* Female patients of childbearing potential must have negative results from two urine or serum pregnancy tests with a sensitivity of at least 50 mIU/mL before a prescription is given. The first test is to be performed at the office visit when the patient is qualified for therapy by her prescriber. The second test is to be performed on the second day of her next menstrual cycle or 11 days after her last unprotected act of sexual intercourse, whichever is later. Additional pregnancy tests are to be conducted monthly during treatment. *Lipids:* Pretreatment and follow-up blood lipids should be obtained under fasting conditions, at least 36 hours after consumption of alcohol. These tests should be performed at weekly or biweekly intervals until the lipid response to Accutane has been established (see **WARNINGS**). *Liver Function Tests:* Baseline and periodic liver function tests should be performed at weekly or biweekly intervals until the response to Accutane has been established (see WARNINGS). *Glucose:* Some patients have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during Accutane therapy, although no causal relationship has been established. *CPK:* Some patients undergoing vigorous physical activity have experienced elevated CPK levels; however, the clinical significance is unknown. *Carcinogenesis, Mutagenesis and Impairment of Fertility:* The Ames test was conducted with and without metabolic activation. The results of the tests in one laboratory were negative white in the second laboratory a weakly positive response (less than 1.6 × background) was noted in *S. typhimurium* TA100 when the assay was conducted with metabolic activation. No dose-response effect was seen and all other strains were negative. Additionally, other tests designed to assess genotoxicity were all negative. In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of isotretinoin of 2, 8 or 32 mg/kg/day. In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day. In general, there was microscopic evidence for appreciable depression of spermatogenesis but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen. In studies of 66 men, 30 of whom were patients with nodular acne under treatment with oral isotretinoin, no significant changes were noted in the count or motility of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years) receiving Accutane therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose. *Pregnancy:* **Category X. See boxed CONTRAINDICATIONS AND WARNINGS.** *Nursing Mothers:* Nursing mothers should not receive Accutane because it is not known if the drug is excreted in human milk. **ADVERSE REACTIONS:** *Clinical Trials and Postmarketing Surveillance:* The adverse reactions listed below reflect the experience from investigational studies, and the postmarketing experience. The relationship of some of these events to therapy is unknown. Many of the side effects and adverse reactions seen in patients receiving Accutane are similar to those described in patients taking very high doses of vitamin A (dryness of the skin and mucous membranes, eg, of the lips, nasal passage, and eyes). *Dose Relationship:* Cheilitis and hypertriglyceridemia are usually dose related. Most adverse reactions reported in clinical trials were reversible when therapy was discontinued; however, some persisted after cessation of therapy (see WARNINGS and ADVERSE REACTIONS). *Body as a Whole:* allergic reactions, including vasculitis, systemic hypersensitivity (see PRECAUTIONS), edema, fatigue, lymphadenopathy, weight loss. *Cardiovascular:* palpitation, tachycardia, vascular thrombotic disease, stroke. *Endocrine/Metabolic:* hypertriglyceridemia (see WARNINGS); alterations in blood sugar levels (see PRECAUTIONS). *Gastrointestinal:* inflammatory bowel disease (see WARNINGS), hepatitis (see WARNINGS), pancreatitis (see WARNINGS), bleeding and inflammation of the gums, colitis, ileitis, nausea, other nonspecific gastrointestinal symptoms. *Hematologic:* allergic reactions (see PRECAUTIONS), anemia, thrombocytopenia, neutropenia, rare reports of agranulocytosis (see PRECAUTIONS). See PRECAUTIONS: *Laboratory Tests* for other hematological parameters. *Musculoskeletal:* skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure (see WARNINGS), mild to moderate musculoskeletal symptoms including arthralgia (see PRECAUTIONS), transient pain in the chest (see PRECAUTIONS), elevations of CPK (see PRECAUTIONS), arthritis, tendinitis, other types of bone abnormalities. *Neurological:* pseudotumor cerebri (see WARNINGS), dizziness, drowsiness, headache, insomnia, lethargy, malaise, nervousness, paresthesias, seizures, stroke, syncope, weakness. *Psychiatric:* suicidal ideation, suicide attempts, suicide, depression, psychosis (see WARNINGS), emotional instability. Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy. *Reproductive System:* abnormal menses. *Respiratory:* bronchospasms (with or without a history of asthma), respiratory infection, voice alteration. *Skin and Appendages:* acne fulminans, alopecia (which in some cases persists), bruising, cheilitis (dry lips), dry mouth, dry nose, dry skin, epistaxis, eruptive xanthomas, flushing, fragility of skin, hair abnormalities, hirsutism, hyperpigmentation and hypopigmentation, infections (including disseminated herpes simplex), nail dystrophy, paronychia, peeling of palms and soles, photoallergic/photosensitizing reactions, pruritus, pyogenic granuloma, rash (including facial erythema, seborrhea, and eczema), sunburn susceptibility increased, sweating, urticaria, vasculitis (including Wegener's granulomatosis; see PRECAUTIONS), abnormal wound healing (delayed healing or exuberant granulation tissue with crusting; see PRECAUTIONS). *Special Senses: Hearing:* hearing impairment (see WARNINGS), tinnitus. *Vision:* corneal opacities (see WARNINGS), decreased night vision which may persist (see WARNINGS), cataracts, color vision disorder, conjunctivitis, dry eyes, eye lid inflammation, keratitis, optic neuritis, photophobia, visual disturbances. *Urinary System:* glomerulonephritis (see PRECAUTIONS), nonspecific urogenital findings (see PRECAUTIONS: *Laboratory Tests* for other urological parameters). *Laboratory:* Elevation of plasma triglycerides (see WARNINGS), decrease in serum high-density lipoprotein (HDL) levels, elevations of serum cholesterol during treatment, increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGTP or LDH (see WARNINGS). Elevation of fasting blood sugar, elevations of CPK (see PRECAUTIONS), hyperuricemia. Decreases in red blood cell parameters, decreases in white blood cell counts (including severe neutropenia and rare reports of agranulocytosis; see PRECAUTIONS), elevated sedimentation rates, elevated platelet counts, thrombocytopenia. White cells in the urine, proteinuria, microscopic or gross hematuria. **OVERDOSAGE:** The oral LD_{50} of isotretinoin is greater than 4000 mg/kg in rats and mice and is approximately 1960 mg/kg in rabbits. In humans, overdosage has been associated with vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness, and ataxia. All symptoms quickly resolved without apparent residual effects.

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Botox Appears To Blunt Migraine Attacks

ASPEN, COLO. — Evidence continues to mount that botulinum toxin A is an effective treatment for migraine headaches, Dr. Arnold Klein said at a surgery seminar sponsored by the Colorado Dermatology Center.

He cited a randomized, double-blind study of botulinum toxin A (Botox) as a preventive therapy for migraines. In that trial, 123 patients with a history of two to eight moderate to severe migraines per month received a single injection of 25 U or 75 U of Botox administered into multiple sites in the pericranial muscles. Controls received placebo injections.

During the 3-month follow-up period, patients who received either dose of Botox reported fewer migraine attacks, milder severity of attacks that did occur, and less use of migraine medications than in the baseline period.

The lower dose of Botox was judged preferable because it was associated with fewer adverse effects.

The authors concluded that pericranial injection of Botox is a safe and effective way to reduce migraine frequency and severity (Headache 40[6]:445-50, 2000).

Many patients who receive Botox for cosmetic reasons later report that their migraines go away, said Dr. Klein, who practices in Beverly Hills.

He advised using slightly higher doses in patients under age 40 years, because the effect seems to wear off more quickly in younger people.

—Norra MacReady