## Physical Activity Offset Effect of 'Obesity Genes'

BY MARY ANN MOON Contributing Writer

wo gene variants were found to confer risk for obesity, but that risk was offset by an intensely physical lifestyle in a study of an Amish community. The findings suggest that in people genetically predisposed to obesity, high levels

of physical activity can blunt that predisposition, said Evadnie Rampersaud, Ph.D., of the University of Maryland, Baltimore,

and her associates. They performed DNA analysis of blood samples from an Old Order Amish population in Pennsylvania. The 704 subjects had also provided an objective measurement of physical activity by wearing an activity monitor for 1 week.

Members of the order eschew many modern conveniences and their daily lives tend to be physically demanding. Their mean age was 44 years. Prevalence of overweight was 54% and of obesity, 10%, in men; and 64% and 30%, respectively, in women.

The researchers analyzed 92 single-nucleotide polymorphisms (SNPs) located in an interval that spanned the FTO (fat mass and obesity-associated) gene and found two that significantly correlated with obesity. One of these, the A allele for rs1861868, was already known to confer a predisposition for obesity. The second SNP, the C allele of rs1477196, has not been associated with obesity before, they said (Arch. Intern. Med. 2008;168:1791-7).

When the subjects were stratified by

level of physical activity, these variants were significantly associated with greater body mass index only in the 361 subjects with low levels of physical activity. High levels of physical activity in the remaining subjects seemed to blunt the association between the two alleles and obesity.

Mean activity levels in the high-activity group were about 900 kcal greater than those in the low-activity group, corresponding to about 3-4 hours of moderately intensive daily activity.

## EFFEXOR XR<sup>®</sup> EXTENDED BRIEF SUMMARY. See package insert for full prescribing information. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll free at 1-800-934-5556. Suicidality and Antidepressant Drugs Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFEXOR XM or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did noi show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in Trance rules risk with the clinical need. Short-term studi ow an increase in the risk of suicidality with antid pared to placebo in adults beyond age 24; there was a r k with antidepressants compared to placebo in adults ar ler. Depression and certain other psychiatric disc mselves associated with increases in the risk of suicide. ages who are started on antidepressant therapy nitored appropriately and observed closely for clinical -cidality, or unusual changes in behavior. Families and uld be advised of the need for close observa munication with the prescriber. EFFEXOR XR is not ap in pediatric patients. (See WARNINGS: Clinical Wors clde Risk, PRECAUTIONS: Information for Patie EXAUTIONS: Pediatric Use.)

PRECAUTIONS: Pediatric Use.) CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). WARNINGS: Clinical Worsening and Suicide Risk.—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these along-standing concern, however, that antidepressants may have a role in along-numersion of depression and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homession and the memorence of suicidality in certain funduring worsening of homessin a

The Defavor, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been aducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Proled analyses of short-term placebo-controlled trials of antidepressant drugs (SMBI and others) showed that these drugs increase the risk of suicidal ity in certain placebo-controlled trials of antidepressants compared to placebo in adults aged 16-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults aged 56 and otder. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive-compulsive disorder (UCO), or other psychiatric disorders included a total of 24 short-term trials (median disorder (UCO), or other psychiatric disorder in the antipasse of placebo in adults aged 55 and other. The pooled analyses of placebo in adults aged 56 short-term trials (median disorder (UCO) or other psychiatric disorder included a total of 24 short-term trials (median disorder) and the provide in ratio of a santidepression disorder (UCO) or adverted to the adult trials in adults and there adult trials in adults and adverted are provided in table of the full prescribing information. No suicides occurred in any of the ediatic trials. There exists differences (drug-placebo difference in the number of cases of suicidality psychiatric disorder) are provided in table of the full prescribing information. No suicides occurred in any of the ediatic trials. There were suicides in the adult trials but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality is a suppresent precure degression adults with adult

is of discontinuing treatment with an MAUL at lease allowed after stopping venlafaxine before starting n Syndrome. The development of potentially life-liferated of serotoneric drugs and (i) with drugs that impair metabolic CONTRAINDICATIONS—MAOIs. If concomitant treatment n SSRI, SNRI, or a 5-hydroxytrybamine receptor agonist (trub anted, careful observation of the patient is advised, particular interval observation of the patient is advised, particular Jumming use of serotonerup. Grown S. MADIS). It Concernation (see CONTRAINDICATIONS — MADIS). It Concernations and the service of the service

eatment with Effexor XR. Abrupt discontinuation or dose reduction of faxine at various doses is associated with new symptoms, the frequency of increased with increased dose level and longer duration of treatment, toms include agitation, ancrexia, anxiety, confusion, coordination impaired, ea, dizziness, dry mouth, dysphoric mood, emotional lability, letitargy, nausea, increased with an emotional lability, letitargy, nausea, increased with ancreased biotheraped ion marghenesis sympto-es beataches, hypomania, incomna, irritability, letitargy, nausea, increased biotheraped ion praceflexistics. Interpreter Head Construction of the second seco

gic phenomena; or 4) if they have a history of glaucoma or pressure. Laboratory Tests—No specific laboratory ed. Drug Interactions—Alcohot: A single dose of ethat e pharmacokinetics. (PK) of veniafaxine or O-desmethy

ventariane will cimetidine to patients with pre-existing hypertension or he dystunction, and the elderly. *Diazepanr.* A single dose of diazepanr did not ap to affect the PK of either ventatiaxine or ODV Ventataxine did not have any e on the PK of diazepanr or its active metabolite, desmethyldiazepanr. *Haloper* Ventataxine decreased total oral-dose clearance of haloperiod, resulting in a increase in haloperiod I AUC. The haloperiod C<sub>mm</sub> increased 8%, but haloperiod elimination half-life was unchanged. Lifetimer A. to affect the PK of either ventalaxine or ODV. Ventalaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyvidiazepam, or affect the psychomotor and psychometric effects induced by diazepam. *Haloperidol* Ventalaxine decreased total oral-dose clarance of haloperidol resulting in a 70% increase in haloperidol AUC. The haloperidol **C**<sub>max</sub> increased 88%, but the haloperidol elimination half-life was unchanged. *Liftium:* A single dose of liftium did not appear to affect the PK of either ventalaxine or ODV. Ventalaxine had no effect on the PK of liftium. *Drugs Highly Bound to Plasma Proteins*: Ventalaxine is not highly bound to plasma proteins; coadministration of Effeor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. *Drugs That Interfere with Hemostasis*: Epidemiological studies that have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspinir may potentiate this risk of bleeding. Increased bleeding has been reported when SSRIs and SNRIs are coadministered with warfarin. *Drugs That Inhibit Cytochrome P450 Isoenzymes*: CYP206 Inhibitors. Ventalaxine is metabolized to its active metabolite, 00V, by CYP206 unbibitor. A pharmacokinetic study with ketoconazole 100 mg b.1.d. with a single dose of ventalaxine and -desemethylventalaxine and DUV. Wo dosage adjustment is required when ventalaxine is coadministered with a 2-01-disage fragmane. Studies a CYP204 inhibitors and ventalaxine may increase levels of ventalaxine and UV. Herefore, cultion is advised if a patient's therapy includes a CYP204 inhibitors and ventalaxine may increase levels of ventalaxine and UV. Herefore, cultion is advised if a patient's therapy includes a CYP204 inhibitors and ventalaxine is a relatively weak inhibitor of CYP205. Ventalaxine did not inhibit CYP142 and CYP34. CYP20 (in Vitro), CYP205. Ventalaxine did not

nes the MRHD (mg/m basis) revealed no inationmations in offspring. However, rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase stillborn pups, and an increase in pup deaths during the first 5 days of lacation end desing began during prepanaty and continued until weight, an increase stillborn pups, and an increase in pup deaths during the first 5 days of lacation eghancy only if clearly needed. *Monteratogenic Effects*: Neonates exposed to lever XR late in the third timester have developed complications requiring olonged hospitalization, respiratory support, and tube feeding. Complications n arise immediately upoh delivery. Hepotrs include respiratory distress, anosis, annea, seizures, temperature instability, feeding difficulty, vomiting, document, and the interst respiratory support, and tube feeding. Complications regulary only if clearly needed. *Monteratogenic Effects*. Neonates exposed to is confinuation synthetic and delivery. Hepotres, include respiratory distress, anosis, annea, seizures, temperature instability, feeding difficulty, vomiting, documentation syntheme in some cases, it is consistent with seriotonin syntheme her treating a pregnant woman with a direct with effect of SNRIs or a drug perilary consider the potential risks and bernettis of treatment and consider pering effector XR in the third timester. Labor, Delivery, Nursing—The effect on rand delivery in hurans is unknown. Venalatane and ODV have been portate of the drug to the mother. Pediatric Use—Salet and effectiveness in pediatic population have not been estabilishe (see BOX WANNING and equative) assessed the impact of Effector XR on directiones have equately assessed the impact of Effector XR on the leight and effectiveness in pediatic population have not been estabilishe (see BOX WANNING and equative) assessed the impact of Effector XR on growth, development, and anges in Weight, Should the decision be made to treat a pediatic patient with evor XR, regular monitoring of weight and height tis recommended du and the second secon

ients; "infrequent"=1/100 to 1/1000 patients; "rare" tients. **Body as a whole** - Frequent: chest pain substema Infrequent: face edema, intentional injury, malaise, mc Nicc pain, pholosensitivity reaction, suicide attempt Rare: appendicitis, bacterenia, carcinoma, cellulitis cular system - Frequent: micraine, tarchivraritia Infere (mainly cold feet and/or cold hands), postular h aneurysm, arteritis, first-degree atrioventricular block, capillary fragility, cerebral ischemia, corr heart failure, heart arrest hematima, cardious Arunculosis, hirsutism, leukoderma, miliara, petecm rash, vesiculobullous rash, seborrhea, skin atrophy, sweating decreased. Special senses - Frequent: ab mydriasis, taste perversion, finrequent: conjunctivitis oftis media, parosmia, photophobia, taste loss; chromatopsia, conjunctival edema, comeal lesion, hemorrhage, glaucoma, retinal hemorrhage, su hyperacusis, keratitis, labyrinthitis, miosis, papilledem albuminuria, urination impaired; Infrequent: am hematuria, kindeny calculus, kindeny pain, leukorrhea nocturia, breast pain, polyuria, prostaite, do postate, and prostate, and prostate infrequenti incontiner urgenov, vaginal, hemorrhage, vagintis; Rare; abort vaginal hemorrhage, vaginitis; Ran ast discharge, breast engorgement ictation, fibrocystic breast, calcium c rgency Verinitical accivitation, including torsates de polities, soute epidi necrolysis/Stevens-Johnson syndrome, erythema multitorme, extraprix symptoms (including dyskinesia and tardive dyskinesia), angle-closure glau hemorrhage (including eye and gastrointestinal bleeding), hepatic e (including GGT elevation; abnormatiles of unspecified liver function tests damage, necrossis, or failure, and fatty liver, interstital land glasaes, invol-movements, LDH increased, neuroleptic malignant syndrome-like events (incr a case of a 10-year-old who may have been taking methylphenidate, was and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, prolactin increased, renal failure, mabdomyolysis, serotonin syndrome, sho electrical sensations or tinnitus (in some cases, subsequent to the discontin of ventazione or tapering of dose), and StADI (usual) in the elderty). El clozapine levels that were temporally associated with adverse events, incr seizures, have been reported following the addition of ventazione. Detaita thermotoplastin time, or NIR have been reported pentation was given to patients on warrain therapy DRUG ABUBE DEPENDENCE: Effixor XR is not a controlled substance. Evaluate patients ca for history of fung abuse and observe such patients closely for signs of miss abuse. **OVERDOSAGE**: The most commonly reported events in overdosage i tachycardia, changes in level of consciousness (ranging from somoher coma), mydrais, seizures, adve, and vonting, Electrogaritors in overdosage i tachycardia, total turbry and a hundle branch block, ORS prolongation/), vent tachycardia, totalycardia, hybolersion, rhadoumyolysis, vertion, invertios, levelso, liter returb, liter testion, interval, burdle branch block, ORS prolongation, vent

Lactivacrial, changes in level of consciousness (ranging from somno-coma), mydriasis, seizures, and vomiting. Electrocardiogram chan prolongation of CI interval, bundle branch block, CHS prolongation, ve tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver serotonin syndrome, and death have been reported. Published retro studies report that ventafaxine overdosage may be associated with an in risk of ratal outcomes compared to that observed with SSI antide products, but lower than that for throyclic antidepressants. Epidemiologic and increased risk of fatal outcomes can be attributed to the toxicity of ve is not clear. Ineatimes that out and the studies of the social of ventilative-treated is not clear. Ineatimes thould consist of those general measures employ management of overdosage with any antidepressant. Ensures employ In overlossing as one of the construction of t

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