Impaired Metabolism, Obesity Double-Team OA

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CHICAGO — The presence of an impaired metabolism exacerbates the impact of obesity as a risk factor for developing knee osteoarthritis and is associated with reduced physical functioning, Mary Fran Sowers, Ph.D., reported at the 2004 World Congress on Osteoarthritis.

Such findings suggest that "the role of obesity with respect to osteoarthritis and functioning may extend mechanistically beyond that of just simple joint loading," said Dr. Sowers, an epidemiology professor at the University of Michigan, Ann Arbor.

Current OA treatments should be evaluated for their potential to exacerbate these metabolic derangements, because this exacerbation is likely to diminish treatment efficacy.

"An understanding of the added contribution of the obesity subtypes could be very useful in guiding primary and secondary treatment efforts," Dr. Sowers added at the meeting, sponsored by the Osteoarthritis Research Society International.

Researchers have identified several obesity subtypes, including individuals who are obese but metabolically healthy. This may occur in about 20% of obese persons and is characterized by large amounts of fat mass but normal insulin levels and favorable cardiovascular risk factor profiles.

Another risk group comprises individuals of normal weight but who have metabolic profiles more typically seen in the obese.

This risk group may account for about 15% of the general population and is characterized by low HDL cholesterol, higher triglyceride levels, and higher levels of inflammatory markers.

A community-based cohort of 775 women aged 43-53 years was evaluated for metabolic obesity, defined on the basis of three body mass index (BMI) cutoff points and the presence of two or more of the following metabolic derangements: diabetes or fasting glucose greater than 125 mg/dL, serum C-reactive protein greater than 2 mg/L, HDL less than 45 mg/dL, triglycerides greater than 200 mg/dL, or a waist-hip ratio greater than 0.81 cm.

The investigators found that 34% of the women were not obese (BMI less than 26 kg/m^2) and had no metabolic derangements.

The risk of knee OA was three times higher in overweight or obese women and nine times higher in very obese women who had metabolic derangement.

Another 31% of the participants were overweight to obese (BMI 26-34 kg/m^2) without a metabolic derangement, and an additional 15% were overweight/obese women who did have a metabolic derangement.

Finally, 12% were very obese (BMI greater than 34 kg/m^2) without a metabolic derangement, and 8% were very obese women who did have a metabolic derangement.

Among those without a metabolic derangement, the odds of having knee OA were increased among women who were either overweight/obese (odds ratio 1.9) or very obese (OR 7.0), compared with women who were not obese and had no metabolic derangement.

But when obesity was associated with a metabolic derangement, the risk of knee OA was three times higher in overweight or obese women (OR 3.3) and nine times higher in very obese women (OR 9.0), compared with women who were not obese and had no metabolic derangement.

The impact of metabolic disorders and weight on OA risk was consistent across all four of the physical tests: speed measured during walking on gait mats, grip strength, timed walk, and timed stair climbing, Dr. Sowers said.

There was no loss in leg strength unless women had an impaired metabolism, and then the loss was most pronounced in individuals with the highest BMI.

Dr. Sowers proposed that metabolic disorders and obesity may affect leg strength by altering glycation products in the muscles, by allowing fatty infiltration of muscle tissue and compromising selective muscle fibers, or by causing innervation problems. ■

PROVIGIL® (modafinil) TABLETS [C-IV]

BRIEF SUMMARY: Consult Package Insert for Complete Prescribing Information

CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL or its inactive ingredients.

WARNINGS: Patients with abnormal levels of sleepiness who take PROVIGIL should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking PROVIGIL, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Prescribers should also be aware that patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.

PRECAUTIONS: ***Diagnosis of Sleep Disorders:*** PROVIGIL should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of either narcolepsy, OSAHS, and/or SWSD has been made in accordance with ICSD or DSM diagnostic criteria. Such an evaluation usually consists of a complete history and physical examination, and it may be supplemented with testing in a laboratory setting.

CPAP Use in Patients with OSAHS: In OSAHS, PROVIGIL is indicated as an adjunct to standard treatment(s) for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating PROVIGIL. If PROVIGIL is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

General: Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities.

Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Alternative or concomitant methods of contraception are recommended during and for 1 month after discontinuation of PROVIGIL.

Cardiovascular System: In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspnea and transient ischemic T-wave changes on ECG were observed in three subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. Such signs may include but are not limited to ischemic ECG changes, chest pain, or arrhythmia.

Patients with a recent history of MI or unstable angina should be treated with caution.

Blood pressure monitoring in short-term controlled trials showed no clinically significant changes in mean systolic and diastolic blood pressure in patients receiving PROVIGIL as compared to placebo. However, a greater proportion of patients on PROVIGIL required new or increased use of antihypertensive medications (2.4%) compared to patients on placebo (0.7%). The differential use was slightly larger when only studies in OSAHS were included, with 3.4% of patients on PROVIGIL and 1.1% of patients on placebo requiring such alterations in the use of antihypertensive medication. Increased monitoring of blood pressure may be appropriate in patients on PROVIGIL.

Central Nervous System: There have been reports of psychotic episodes associated with PROVIGIL use. One healthy male volunteer developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of PROVIGIL and sleep deprivation. There was no evidence of psychosis 36 hours after drug discontinuation. Caution should be exercised when PROVIGIL is given to patients with a history of psychosis.

Patients with Severe Renal Impairment: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modafinil acid, but not PROVIGIL itself.

Patients with Severe Hepatic Impairment: PROVIGIL should be administered at a reduced dose because its clearance is decreased.

Elderly Patients: Elderly patients may have diminished renal and/or hepatic function; therefore, dosage reduction should be considered.

Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL.

PROVIGIL is indicated for patients who have abnormal levels of sleepiness. PROVIGIL has been shown to improve, but not eliminate this abnormal tendency to fall asleep. Therefore, patients should not alter their previous behavior with regard to potentially dangerous activities (eg, driving, operating machinery) or other activities requiring appropriate levels of wakefulness, until and unless treatment with PROVIGIL has been shown to produce levels of wakefulness that permit such activities. Patients should be advised that PROVIGIL is not a replacement for sleep.

Patients should be informed that it may be critical that they continue to take their previously prescribed treatments (eg, patients with OSAHS receiving CPAP should continue to do so).

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking PROVIGIL.

Pregnancy: Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation of therapy.

Nursing: Patients should notify their physician if they are breast feeding.

Concomitant Medication: Patients should inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, because of the potential for drug interactions.

Alcohol: It is prudent to avoid alcohol while taking PROVIGIL.

Allergic Reactions: Patients should notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Drug Interactions: ***CNS Active Drugs:*** In a single-dose study, simultaneous administration of PROVIGIL 200 mg with *methylphenidate* 40 mg delayed the absorption of PROVIGIL by approximately 1 hour.

In a single-dose study, simultaneous administration of PROVIGIL 200 mg with *dextroamphetamine* 10 mg delayed absorption of PROVIGIL by approximately 1 hour.

Coadministration of a single dose of *clomipramine* 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of either drug. One incident of increased levels of *clomipramine* and its active metabolite desmethylclomipramine has been reported.

In the drug interaction study between PROVIGIL and ethinyl estradiol (EE_2), on the same days as those for the plasma sampling for EE_2 pharmacokinetics, a single dose of *triazolam* 0.125 mg was also administered. Mean C_{max} and AUC_0- of *triazolam* were decreased by 42% and 59%, respectively, and its elimination half-life was decreased by approximately an hour after the modafinil treatment.

In the absence of interaction studies with monoamine oxidase (MOA) inhibitors, caution should be exercised.

Other Drugs: No significant changes in the pharmacokinetics of *warfarin* occurred in healthy subjects given 1 dose of *warfarin* 5 mg following chronic administration of PROVIGIL. However, more frequent monitoring of prothrombin times/INR is advised when PROVIGIL is coadministered with *warfarin*.

PROVIGIL once daily 200 mg/day for 7 days followed by 400 mg/day for 21 days decreased *ethinyl estradiol* C_{max} and $AUC_{0\text{-}24}$ by a mean 11% and 18% with no apparent change in the elimination rate.

One interaction between PROVIGIL and *cyclosporine* has been reported in a 41-year-old female. After 1 month of PROVIGIL 200 mg/day, *cyclosporine* blood levels decreased by 50%. Dosage adjustment for *cyclosporine* may be needed.

Potential Interactions with Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes: In primary human hepatocytes, PROVIGIL slightly induced CYP1A2, CYP2B6 and CYP3A4 in a dose-dependent manner. *In vitro* experiments do not necessarily predict response *in vivo;* caution should be exercised when PROVIGIL is coadministered with drugs that are metabolized by enzymes.

In human hepatocytes, PROVIGIL produced a dose-related suppression of CYP2C9 activity suggesting a potential for metabolic interaction between PROVIGIL and substrates of this enzyme (eg, S-warfarin and phenytoin). In healthy volunteers, chronic PROVIGIL treatment had no significant effect on single-dose pharmacokinetics of warfarin vs placebo.

In human liver microsomes, PROVIGIL and modafinil sulfone reversibly inhibited CYP2C19. Both compounds combined could produce sustained partial enzyme inhibition. Drugs largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin (also via CYP2C9) or S-mephenytoin may have prolonged elimination with PROVIGIL coadministration and may require dose reduction and monitoring for toxicity.

CYP2C19 provides ancillary metabolism of some tricyclic antidepressants (eg, clomipramine and desipramine) primarily metabolized by CYP2D6. In tricyclic users deficient in CYP2D6, CYP2C19 metabolism may be substantially increased. PROVIGIL may elevate tricyclics in this patient subset. A reduction in tricyclic dose may be needed.

Due to partial involvement of CYP3A4 elimination of PROVIGIL, coadministration of potent inducers of CYP3A4 (eg, carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg, ketoconazole, itraconazole) could alter modafinil plasma levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** The highest dose studied in carcinogenesis studies represent 1.5 times (mouse) or 3 times (rat) the maximum human daily dose of 200 mg on a mg/m^2 basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the carcinogenic potential in that species has not been fully evaluated.

Mutagenesis: There was no evidence of mutagenic or clastogenic potential of PROVIGIL.

Impairment of Fertility: PROVIGIL was administered orally to male and female rats prior to and throughout mating and gestation at up to 23 times the recommended human dose of 200 mg/day on a mg/m^2 basis with no effect on fertility.

Pregnancy: Pregnancy Category C: PROVIGIL administered orally to pregnant rats throughout the period of organogenesis caused, in the absence of maternal toxicity, an increase in resorptions and an increased incidence of hydronephrosis and skeletal variations in the offspring at a dose of 200 mg/kg/day (10 times the recommended human dose of 200 mg/day on a mg/m^2 basis) but not at 100 mg/kg/day. However, in a subsequent study of up to 480 mg/kg/day (23 times the recommended human dose on a mg/m^2 basis), which included maternally toxic doses, no adverse effects on embryofetal development were seen.

PROVIGIL administered orally to pregnant rabbits throughout the period of organogenesis at doses up to 100 mg/kg/day (10 times the recommended human dose on a mg/m^2 basis) had no effects on embryofetal development.

However, in a subsequent study in pregnant rabbits, increased resorptions, and increased alterations in fetuses from a single litter (open eye lids, fused digits, rotated limbs), were observed at 180 mg/kg/day (17 times the recommended human dose on a mg/m^2 basis), a dose that was also maternally toxic.

PROVIGIL administered orally to rats throughout gestation and lactation at doses up to 200 mg/kg/day (5 times the recommended human dose on a mg/m^2 basis), had no effects on the postnatal development of the offspring. There are no adequate and well-controlled studies in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated.

Nursing Mothers: It is not known whether PROVIGIL or its metabolites are excreted in human milk. Caution should be exercised when PROVIGIL is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in individuals below 16 years of age have not been established. Leukopenia has been reported in pediatric patients taking PROVIGIL.

GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established.

ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 3500 patients, of whom more than 2000 patients with excessive sleepiness associated with primary disorders of sleep and wakefulness were given at least 1 dose of PROVIGIL. In clinical trials, PROVIGIL has been found to be generally well tolerated and most adverse experiences were mild to moderate.

The most commonly observed adverse events (5%) associated with the use of PROVIGIL more frequently than placebo-treated patients in the placebo-controlled clinical studies in primary disorders of sleep and wakefulness were headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia.

In the placebo-controlled clinical trials, 8% of the 934 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (2%), nausea, anxiety, dizziness, insomnia, chest pain, and nervousness (each <1%).

The incidence of adverse experiences that occurred at a rate of 1% and were more frequent in patients treated with PROVIGIL than in placebo patients in the principal trials are listed below. Consult full prescribing information on adverse events.

Body as a Whole: Headache, back pain, flu syndrome, chest pain, chills, neck rigidity
Cardiovascular: Hypertension, tachycardia, palpitation, vasodilatation
Digestive: Nausea, diarrhea, dyspepsia, dry mouth, anorexia, constipation, abnormal liver function, flatulence, mouth ulceration, thirst
Hemic/Lymphatic: Eosinophilia
Metabolic/Nutritional: Edema
Nervous: Nervousness, insomnia, anxiety, dizziness, depression, paresthesia, somnolence, hypertonia, dyskinesia, hyperkinesia, agitation, confusion, tremor, emotional lability, vertigo
Respiratory: Rhinitis, pharyngitis, lung disorder, epistaxis, asthma
Skin/Appendages: Sweating, herpes simplex
Special Senses: Amblyopia, abnormal vision, taste perversion, eye pain
Urogenital: Urine abnormality, hematuria, pyuria

Dose Dependency: In the placebo-controlled clinical trials the only adverse events that were clearly dose related were headache and anxiety.

Vital Sign Changes: While there was no consistent change in mean values of heart rate or systolic and diastolic blood pressure, the requirement for antihypertensive medication was slightly greater in patients on PROVIGIL compared to placebo.

Weight Changes: There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo-treated patients.

Laboratory Changes: Mean plasma levels of gamma glutamyltransferase (GGT) and alkaline phosphatase (AP) were higher following administration of PROVIGIL, but not placebo. Few subjects, however, had GGT or AP elevations outside of the normal range. Shifts to higher, but not clinically significantly abnormal, GGT and AP values appeared to increase with time on PROVIGIL. No differences were apparent in alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin.

ECG Changes: No treatment-emergent pattern of ECG abnormalities was found in placebo-controlled clinical trials following administration of PROVIGIL.

Postmarketing Reporting: In addition to the adverse events observed during clinical trials, the following adverse events have been identified during post-approval use of PROVIGIL in clinical practice. Because these adverse events are reported voluntarily from a population of uncertain size, reliable estimates of their frequency cannot be made.

Hematologic: Agranulocytosis
Central Nervous System: Symptoms of psychosis, symptoms of mania
Hypersensitivity: Urticaria (hives), angioedema

DRUG ABUSE AND DEPENDENCE: ***Abuse Potential and Dependence:*** In addition to its wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants. *In vitro,* PROVIGIL binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies, PROVIGIL was also partially discriminated as stimulant-like. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (eg, methylphenidate, amphetamine, or cocaine) abuse. In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). Patients should be observed for signs of misuse or abuse.

Withdrawal: Following 9 weeks of PROVIGIL use in 1 US clinical trial, no specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.

OVERDOSAGE: Human Experience: In clinical trials, a total of 151 protocol-specified doses 1000 mg/day (5 to 8 times the recommended daily dose of 200 mg) have been administered to 32 subjects, including 13 subjects who received doses of 1000 or 1200 mg/day for 7 to 21 consecutive days. In addition, several intentional acute overdoses occurred; the two largest being 4500 mg and 4000 mg taken by two subjects participating in foreign depression studies. None of these study subjects experienced any unexpected or life-threatening effects. Adverse experiences that were reported at these doses included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time.

From post-marketing experience, there have been no reports of fatal overdoses involving PROVIGIL alone (doses up to 12 grams). Overdoses involving multiple drugs, including PROVIGIL, have resulted in fatal outcomes. Symptoms most often accompanying PROVIGIL overdose, alone or in combination with other drugs have included insomnia, restlessness, disorientation, confusion, excitation, hallucination, nausea, diarrhea, tachycardia, bradycardia, hypertension, and chest pain.

Cases of accidental ingestion/overdose have been reported in children as young as 11 months of age. The highest reported accidental ingestion on a mg/kg basis occurred in a three-year-old boy who ingested 800-1000 mg (50-63 mg/kg) of PROVIGIL. The child remained stable. The symptoms associated with overdose in children were similar to those observed in adults.

Overdose Management: No specific antidote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data to suggest the utility of dialysis or urinary acidification or alkalinization in enhancing drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

Manufactured for: **Cephalon, Inc.,** West Chester, PA 19380

For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at **www.PROVIGIL.com**

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