

Smoking Worsens Early Axial Spondyloarthritis

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For patients with spondyloarthritis who smoke, it's never too early to quit, according to new data presented by Dr. Pedro Machado.

An analysis of data on 708 patients in a multicenter study found that patients with axial spondyloarthritis (SpA) who

smoked were more likely than nonsmokers with the disease to have earlier onset of inflammatory back pain, greater disease activity, increased axial inflammation on MRI, increased axial structural damage on MRI and radiographs, poorer function, and worse quality of life.

"Taking into account that smoking is a potentially modifiable lifestyle factor, axial spondyloarthritis patients that smoke should be strongly advised to quit this

habit," Dr. Machado said in an interview.

Previous studies focused on ankylosing spondylitis and showed that smokers had more limited physical function and increased radiographic damage compared with nonsmokers.

The current analysis focused on the early disease stage of axial SpA, said Dr. Machado of Coimbra (Portugal) University Hospital, who is currently a physician-researcher at Leiden (the Nether-

lands) University Center. The analysis of data from the Devenir des Spondylarthropathies Indifférenciées Récente (DESIR) study covered 654 patients who fulfilled criteria for axial SpA on at least one of several criteria sets.

On average, the onset of inflammatory back pain occurred 1.5 years earlier in the 37% of patients who currently smoked compared with nonsmokers, after adjustment. Smoking was associated with significantly higher disease activity scores on the Ankylosing Spondylitis Disease Activity Index (a 0.2-point average worsening on the 10-point scale) and the Bath Ankylosing Spondylitis Disease Activity Index (a 0.5-point average worsening on the 10-point scale), and

features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Warnings and Precautions*].

When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

Lilly maintains a pregnancy registry to monitor the pregnancy outcomes of women exposed to Cymbalta while pregnant. Healthcare providers are encouraged to register any patient who is exposed to Cymbalta during pregnancy by calling the Cymbalta Pregnancy Registry at 1-866-814-6975 or by visiting www.cymbaltapregnancyregistry.com.

Labor and Delivery—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics. (See *Nursing Mothers* section in full PI for additional information.)

Pediatric Use—Safety and effectiveness in the pediatric population have not been established [see *Boxed Warning and Warnings and Precautions*]. Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use—Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1041 patients in CLBP premarketing studies, 21.2% (221) were 65 years of age or over. Of the 487 patients in OA premarketing studies, 40.5% (197) were 65 years of age or over. Of the 1074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Of the 1761 patients in FM premarketing studies, 7.9% (140) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD, DPNP, FM, OA, and CLBP studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Cymbalta, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Warnings and Precautions*]. (See *Geriatric Use* section in full PI for additional information.)

Gender—Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Smoking Status—Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race—No specific pharmacokinetic study was conducted to investigate the effects of race.

Hepatic Insufficiency—[See *Warnings and Precautions-Use in Patients with Concomitant Illness*.] (See *Use in Patients with Concomitant Illness-Hepatic Insufficiency* section in full PI for additional information.)

Severe Renal Impairment—[See *Warnings and Precautions-Use in Patients with Concomitant Illness*.] (See *Use in Patients with Concomitant Illness-Severe Renal Impairment* section in full PI for additional information.)

DRUG ABUSE AND DEPENDENCE: Abuse—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Dependence—In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

OVERDOSAGE: Signs and Symptoms—In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

Management of Overdose—There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug. (See *Management of Overdose* section in full PI for additional information.)

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, and Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m² basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m² basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m² basis) did not increase the incidence of tumors.

Mutagenesis—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 20 mg/day on a mg/m² basis) did not alter mating or fertility.

PATIENT COUNSELING INFORMATION: See FDA-approved Medication Guide and Patient Counseling Information section of full PI.

Additional information can be found at www.Cymbalta.com



Smokers were 54% more likely to have lesions of the sacroiliac joints.

with worse functional status scores on the Bath Ankylosing Spondylitis Functional Index (a 0.4-point average worsening on the 10-point scale).

Among the MRI findings, smokers had a 57% increased likelihood of inflammation of the sacroiliac joints and double the risk for spine inflammation compared with nonsmokers, Dr. Machado and his associates found. Smokers were 54% more likely to show structural lesions of the sacroiliac joints and twice as likely to show structural lesions of the spine on MRI compared with nonsmokers. Modified Stroke Ankylosing Spondylitis Spinal Scores were 0.5 points worse on average in smokers than in nonsmokers, a statistically significant difference.

Health-related quality of life was poorer in smokers than nonsmokers, evidenced by an average 1.4-point worsening on the Ankylosing Spondylitis Quality of Life score, a 5-point worsening on the 36-item Short Form Health Survey (SF-36) physical component score, and a 6-point worsening on the SF-36 mental component score.

The cohort was relatively young (mean age, 34 years; median age, 33 years) with a short duration of symptoms (mean, 1.5 years; median, 1.4 years).

Pfizer, which markets a medication for ankylosing spondylitis, funded the DESIR study with an unrestricted grant and was not involved in the analyses. Dr. Machado said the investigators had no relevant financial disclosures. ■

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