Smoking Tied to Greater Type 2 Diabetes Risk

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Cigarette smoking is associated with an increased risk of developing type 2 diabetes, results of a meta-analysis suggest.

"Active smokers had an increased risk of developing type 2 diabetes, compared with nonsmokers, with a pooled relative risk of 1.44," study investigators reported.

The researchers conducted a meta-analysis of all 25 prospective cohort studies of the issue in the United States, Europe, Japan, and Israel that were published between 1992 and 2006.

All of the studies examined a possible link between smoking and irregularities of glucose metabolism, and all but one found a positive association, Dr. Carole Willi of the University of Lausanne (Switzerland) and her associates wrote.

The number of study subjects ranged from 630 people to more than 700,000 people, for a total of 1.2 million subjects and 45,844 cases of incident diabetes in the meta-analysis. Overall, 35% of the people were current smokers. Follow-up ranged from 5 to 30 years.

The association between smoking and diabetes remained robust through numerous statistical analyses that explored study factors as well as clinical variables. The findings also suggested a dose-response relationship, because the association with diabetes was stronger among heavy smokers than among light smokers, and was stronger in active smokers than in former smokers.

"Given this consistency, we conclude that the relevant question should no longer be whether this association exists, but rather whether this established association is causal," Dr. Willi and her associates said (JAMA 2007;298:2654-64).

"There is theoretical biological plausibility for causality in that smoking may lead to insulin resistance or inadequate

compensatory insulin secretion responses according to several but not all studies," they wrote.

They noted that "Smoking also has a clinical significant effect on both oral and intravenous glucose tolerance tests that could influence diabetes detection."

The adverse effect of smoking on diabetes risk "has been generally underrecognized," Dr. Eric L. Ding and Dr. Frank B. Hu of the Harvard School of Public Health, Boston, said in an editorial accompanying the report.

Dr. Ding and Dr. Hu estimated that 12% of all type 2 diabetes in the United States may be attributable to smoking, based on this study's estimates, statistics on smoking prevalence, and an accepted population-attributable risk formula (JAMA 2007;298:2675-6).

In addition, "an estimated 2.3 million cases of diabetes in the United States and a corresponding $14.9 billion of the annual U.S. $132 billion diabetes cost burden may be attributable to smoking," they said.

Although the exact mechanism by which smoking may contribute to the development of diabetes hasn't been identified, smoking is known to be related to central adiposity, to increase inflammation and oxidative stress, to directly damage beta-cell function, to impair endothelial function, and to impair insulin sensitivity and glucose tolerance, Dr. Ding and Dr. Hu said.

Given the findings of Dr. Willi and her associates, it is "important and prudent for clinicians to screen for and carefully monitor glucose levels among current and former smokers," they added. ■

PHOTODISC

Active smokers had a pooled relative risk of 1.44 for developing type 2 diabetes compared with nonsmokers.

[†] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[‡] Investigator term; summary level term is amblyopia.

Controlled Studies in Postherpetic Neuralgia *Adverse Reactions Leading to Discontinuation* In clinical trials in patients with postherpetic neuralgia, 14% of patients treated with LYRICA and 7% of patients treated with placebo discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness (4%) and somnolence (3%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring in greater frequency in the LYRICA group than in the placebo group, were confusion (2%), as well as peripheral edema, asthenia, ataxia, and abnormal gait (1% each). *Most Common Adverse Reactions* Table 2 lists all adverse reactions, regardless of causality, occurring in ≥1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined LYRICA group for which the incidence was greater in this combined LYRICA group than in the placebo group. In addition, an event is included, even if the incidence in the all LYRICA group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate".

Table 2 Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body System - Preferred term	75 mg/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	3	3	5	3	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system						
Dry mouth	7	7	6	15	8	3
Constipation	4	5	5	5	5	2
Flatulence	2	1	2	3	2	1
Vomiting	1	1	3	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	0	8	16	16	12	4
Weight gain	1	2	5	7	4	0
Edema	0	1	2	6	2	1
Musculoskeletal system						
Myasthenia	1	1	1	1	1	0
Nervous system						
Dizziness	11	18	31	37	26	9
Somnolence	8	12	18	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	2	4	8	4	1
Confusion	1	2	3	7	3	0
Thinking abnormal[†]	0	2	1	6	2	2
Incoordination	2	2	1	3	2	0
Amnesia	0	1	1	4	2	0
Speech disorder	0	0	1	3	1	0
Respiratory system						
Bronchitis	0	1	1	3	1	1
Special senses						
Blurry vision[‡]	1	5	5	9	5	3
Diplopia	0	2	2	4	2	0
Abnormal vision	0	1	2	5	2	0
Eye disorder	0	1	1	2	1	0
Urogenital system						
Urinary incontinence	0	1	1	2	1	0

* PGB: pregabalin
[†] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[‡] Investigator term; summary level term is amblyopia.

Controlled Add-On Studies in Adjunctive Therapy for Adult Patients with Partial Onset Seizures *Adverse Reactions Leading to Discontinuation* Approximately 15% of patients receiving LYRICA and 6% of patients receiving placebo in add-on epilepsy trials discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the adverse reactions most frequently leading to discontinuation were dizziness (6%), ataxia (4%), and somnolence (3%). In comparison, <1% of patients in the placebo group withdrew due to each of these events. Other adverse reactions that led to discontinuation of at least 1% of patients in the LYRICA group and at least twice as frequently compared to the placebo group were asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, and confusion (which each led to withdrawal in 2% or less of patients). *Most Common Adverse Reactions* Table 3 lists all dose-related adverse reactions occurring in at least 2% of all LYRICA-treated patients. Dose-relatedness was defined as the incidence of the adverse event in the 600 mg/day group was at least 2% greater than the rate in both the placebo and 150 mg/day groups. In these studies, 758 patients received LYRICA and 294 patients received placebo for up to 12 weeks. Because patients were also treated with 1 to 3 other AEDs, it is not possible to determine whether the following adverse reactions can be ascribed to LYRICA alone, or the combination of LYRICA and other AEDs. A majority of pregabalin-treated patients in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate".

Table 3 Dose-related treatment-emergent adverse reaction incidence in controlled trials in adjunctive therapy for adult patients with partial onset seizures (Events in at least 2% of all LYRICA-treated patients and the adverse reaction in the 600 mg/day group was ≥2% the rate in both the placebo and 150 mg/day groups)

Body System - Preferred term	150 mg/d [N=185] %	300 mg/d [N=90] %	600 mg/d [N=395] %	All PGB* [N=670][†] %	Placebo [N=294] %
Body as a whole					
Accidental injury	7	11	10	9	5
Pain	3	2	5	4	3
Digestive system					
Increased appetite	2	3	6	5	1
Dry mouth	1	2	6	4	1
Constipation	1	1	7	4	2
Metabolic and nutritional disorders					
Weight gain	5	7	16	12	1
Peripheral edema	3	3	6	5	2
Nervous system					
Dizziness	18	31	38	32	11
Somnolence	11	18	28	22	11
Ataxia	6	10	20	15	4
Tremor	3	7	11	8	4
Thinking abnormal[‡]	4	8	9	8	2
Amnesia	3	2	6	5	2
Speech disorder	1	2	7	5	1
Incoordination	1	3	6	4	1
Abnormal gait	1	3	5	4	0
Twitching	0	4	5	4	1
Confusion	1	2	5	4	2
Myoclonus	1	0	4	2	0
Special senses					
Blurred vision[§]	5	8	12	10	4
Diplopia	5	7	12	9	4
Abnormal vision	3	1	5	4	1

* PGB: pregabalin
[†] Excludes patients who received the 50 mg dose in Study E1 (included in full prescribing information).
[‡] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[§] Investigator term; summary level term is amblyopia.

Controlled Studies with Fibromyalgia *Adverse Reactions Leading to Discontinuation* In clinical trials of patients with fibromyalgia, 19% of patients treated with pregabalin (150–600 mg/day) and 10% of patients treated with placebo discontinued prematurely due to adverse reactions. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness (6%) and somnolence (3%). In comparison, <1% of placebo-treated patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin treatment group than in the placebo treatment group, were fatigue, headache, balance disorder, and weight increased. Each of these adverse reactions led to withdrawal in approximately 1% of patients. *Most Common Adverse Reactions* Table 4 lists all adverse reactions, regardless of causality, occurring in ≥2% of patients with fibromyalgia in the 'all pregabalin' treatment group for which the incidence was greater than in the placebo treatment group. A majority of pregabalin-treated patients in clinical studies experienced adverse reactions with a maximum intensity of "mild" or "moderate".

Table 4 Treatment-emergent adverse reaction incidence in controlled trials in Fibromyalgia (Events in at least 2% of all LYRICA-treated patients and occurring more frequently in the all pregabalin-group than in the placebo treatment group)

System Organ Class - Preferred term	150 mg/d [N=132] %	300 mg/d [N=502] %	450 mg/d [N=505] %	600 mg/d [N=378] %	All PGB* [N=1517] %	Placebo [N=505] %
Ear and Labyrinth Disorders						
Vertigo	2	2	2	1	2	0
Eye Disorders						
Vision blurred	8	7	7	12	8	1
Gastrointestinal Disorders						
Dry mouth	7	6	9	9	8	2
Constipation	4	4	7	10	7	2
Vomiting	2	3	3	2	3	2
Flatulence	1	1	2	2	2	1
Abdominal distension	2	2	2	2	2	1
General Disorders and Administrative Site Conditions						
Fatigue	5	7	6	8	7	4
Edema peripheral	5	5	6	9	6	2
Chest pain	2	1	1	2	2	1
Feeling abnormal	1	3	2	2	2	0
Edema	1	2	1	2	2	1
Feeling drunk	1	2	1	2	2	0
Infections and Infestations						
Sinusitis	4	5	7	5	5	4
Investigations						
Weight increased	8	10	10	14	11	2
Metabolism and Nutrition Disorders						
Increased appetite	4	3	5	7	5	1
Fluid retention	2	3	3	2	2	1
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	4	3	3	6	4	2
Muscle spasms	2	4	4	4	4	2
Back pain	2	3	4	3	3	3
Nervous System Disorders						
Dizziness	23	31	43	45	38	9
Somnolence	13	18	22	22	20	4
Headache	11	12	14	10	12	12
Disturbance in attention	4	4	6	6	5	1
Balance disorder	2	3	6	9	5	0
Memory impairment	1	3	4	4	3	0
Coordination abnormal	2	1	2	2	2	1
Hypoaesthesia	2	2	3	2	2	1
Lethargy	2	2	1	2	2	0
Tremor	0	1	3	2	2	0
Psychiatric Disorders						
Euphoric Mood	2	5	6	7	6	1
Confusional state	0	2	3	4	3	0
Anxiety	2	2	2	2	2	1
Disorientation	1	0	2	1	2	0