Glucose Tolerance Tests Urged for All With PCOS

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Because of their increased risk of developing impaired glucose tolerance and type 2 diabetes, all women with polycystic ovary syndrome should be screened with a 2-hour oral glucose tolerance test, and that test should be repeated every 2 years, according to a statement from the Androgen Excess Society.

The position statement was developed by an expert multidisciplinary panel from the Medical College of Virginia, Virginia Commonwealth University, Richmond, which conducted a systematic review of the published, peer-reviewed medical literature on the prevalence and risk factors for impaired glucose tolerance in women with polycystic ovary syndrome (J. Clin. Endocrinol. Metab. 2007;92:4546-56).

The recommendation for a full oral glucose tolerance test (OGTT) for all patients with polycystic ovary syndrome (PCOS) goes beyond screening recommendations issued by other professional organizations. Most recommend it only in obese women with PCOS or those with a family history of type 2 diabetes or insulin resistance.

The panel focused on studies indicating that both lean and obese women with PCOS are at increased risk of developing impaired glucose tolerance and diabetes. It also noted that a number of studies show that a finding of impaired fasting glucose is not a useful substitute for an OGTT, because about a third of individuals with type 2 diabetes have normal fasting glucose. Furthermore, impaired glucose tolerance, but not impaired fasting glucose, is a strong predictor of cardiovascular disease and premature mortality.

"The position statement makes a valuable contribution to the health care of women with PCOS by recognizing its strong association with insulin resistance and type 2 diabetes," Dr. Rhoda H. Cobin said in an interview. Dr. Cobin, a past pres-

ident of both the American College of Endocrinology and the American Association of Clinical Endocrinologists (AACE), chaired the panel that developed the AACE's 2005 PCOS position statement (Endocr. Pract. 2005;11:126-34).

However, an oral glucose tolerance test may not be feasible in all clinical settings, which is why "the AACE statement did not make it mandatory but, based on the same evidence, settled for the directive to look for type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance in all PCOS women, using whatever method possible," Dr. Cobin said. "I [agree] that not only obese women should be tested, but that lean PCOS women may have insulin resistance and diabetes, while obesity exacerbates the situation."

The position statement from the Androgen Excess Society (AES) notes that several AES board members disagreed with the recommendation to screen all women with PCOS with an OGTT. The minority report says evidence on the risk of impaired glucose tolerance in lean PCOS women is "limited and still emerging." Those board members recommended an OGTT only in PCOS patients whose body mass index was 30 kg/m^2 or more or who had at least one additional risk factor for diabetes including advanced age, family history of diabetes, or a personal history of gestational diabetes.

The AES statement makes several recommendations on the prevention, screening, and treatment of impaired glucose tolerance in patients with PCOS. It suggested the OGTT be repeated once every 2 years or even earlier if the patient has additional risk factors. Patients with impaired glucose tolerance should be screened annually for the development of diabetes.

Intensive lifestyle modification and weight loss should be the mainstay of treatment for all patients with PCOS and impaired glucose tolerance. Insulin-sensitizing agents such as metformin and the thiazolidinediones should also be considered.

The panel also recommended that adolescents with PCOS should, like their adult counterparts, be screened with an OGTT every 2 years and should be treated with intensive lifestyle modification, including diet and moderate exercise. Insulin-sensitizing agents should be considered, but should not be mandated until there have been well-designed, randomized controlled trials demonstrating their efficacy.

Dr. Cobin said she saw few arguments against the OGTT recommendations. "The only negatives are inconvenience and [to a small degree] cost [but] the cost factor is far outweighed by the cost of undiagnosed insulin resistance and diabetes." ■

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† 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