

Options Limited for Adult Women With Acne

BY DAMIAN McNAMARA

EXPERT ANALYSIS FROM A SEMINAR ON
WOMEN'S AND PEDIATRIC
DERMATOLOGY

SAN FRANCISCO – Dermatologists are seeing an increasing incidence of adult women with acne in their offices and they are a clear challenge to treat, Dr. Hilary E. Baldwin said.

Compared to teenagers, women in

their 30s, 40s, and 50s – and their acne lesions – can be more resistant to treatment, Dr. Baldwin said at the seminar, which was sponsored by Skin Disease Education Foundation (SDEF).

“One of the problems of treating moderate to severe acne in the adult woman is that topical medications may not work particularly well. It may be that she is a little harder to treat, but also she has acne on the neck and the jaw, which

is more sensitive skin, and the topical products tend to be quite irritating,” Dr. Baldwin said.

Acne after adolescence also can be more psychosocially devastating. Unlike a teenage girl, an affected woman may have no one else in her social group who has acne. And “because teenagers are supposed to have acne,” Dr. Baldwin said, “people will question: What is she doing wrong? Is she not eating right?”

Acne can have a detrimental effect on sexuality, motherhood, and/or returning to the workplace, and can deepen a midlife crisis, said Dr. Baldwin, who is vice chair of the department of dermatology at the State University of New York, Brooklyn.

With fewer topical agents in their armamentarium for the adult woman with acne, dermatologists tend to prescribe oral medication, Dr. Baldwin said.

reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of treatment-emergent adverse events during LANTUS clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-emergent adverse events in pooled clinical trials up to 28 weeks duration in adults with type 1 diabetes (adverse events with frequency \geq 5%)

	LANTUS, % (n=1257)	NPH, % (n=1070)
Upper respiratory tract infection	22.4	23.1
Infection*	9.4	10.3
Accidental injury	5.7	6.4
Headache	5.5	4.7

*Body System not Specified

Table 2: Treatment-emergent adverse events in pooled clinical trials up to 1 year duration in adults with type 2 diabetes (adverse events with frequency \geq 5%)

	LANTUS, % (n=849)	NPH, % (n=714)
Upper respiratory tract infection	11.4	13.3
Infection*	10.4	11.6
Retinal vascular disorder	5.8	7.4

*Body System not Specified

Table 3: Treatment-emergent adverse events in a 5-year trial of adults with type 2 diabetes (adverse events with frequency \geq 10%)

	LANTUS, % (n=514)	NPH, % (n=503)
Upper respiratory tract infection	29.0	33.6
Edema peripheral	20.0	22.7
Hypertension	19.6	18.9
Influenza	18.7	19.5
Sinusitis	18.5	17.9
Cataract	18.1	15.9
Bronchitis	15.2	14.1
Arthralgia	14.2	16.1
Pain in extremity	13.0	13.1
Back pain	12.8	12.3
Cough	12.1	7.4
Urinary tract infection	10.7	10.1
Diarrhea	10.7	10.3
Depression	10.5	9.7
Headache	10.3	9.3

Table 4: Treatment-emergent adverse events in a 28-week clinical trial of children and adolescents with type 1 diabetes (adverse events with frequency \geq 5%)

	LANTUS, % (n=174)	NPH, % (n=175)
Infection*	13.8	17.7
Upper respiratory tract infection	13.8	16.0
Pharyngitis	7.5	8.6
Rhinitis	5.2	5.1

*Body System not Specified

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• *Severe Hypoglycemia*

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LANTUS [See Warnings and Precautions (5.3)]. Tables 5 and 6 summarize the incidence of severe hypoglycemia in the LANTUS individual clinical trials. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL (\leq 56 mg/dL in the 5-year trial) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

The rates of severe symptomatic hypoglycemia in the LANTUS clinical trials (see Section 14 in the full prescribing information for a description of the study designs) were comparable for all treatment regimens (see Tables 5 and 6). In the pediatric phase 3 clinical trial, children and adolescents with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adult trials with type 1 diabetes. (see Table 5) [See Clinical Studies (14) in the full prescribing information].

Table 5: Severe Symptomatic Hypoglycemia in Patients with Type 1 Diabetes

	Study A Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study B Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study C Type 1 Diabetes Adults 16 weeks In combination with insulin lispro		Study D Type 1 Diabetes Pediatrics 26 weeks In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	10.6 (31/292)	15.0 (44/293)	8.7 (23/264)	10.4 (28/270)	6.5 (20/310)	5.2 (16/309)	23.0 (40/174)	28.6 (50/175)

Table 6: Severe Symptomatic Hypoglycemia in Patients with Type 2 Diabetes

	Study E Type 2 Diabetes Adults 52 weeks In combination with oral agents		Study F Type 2 Diabetes Adults 28 weeks In combination with regular insulin		Study G Type 2 Diabetes Adults 5 years In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	1.7 (5/289)	1.1 (3/281)	0.4 (1/259)	2.3 (6/259)	7.8 (40/513)	11.9 (60/504)

• *Retinopathy*

Retinopathy was evaluated in the LANTUS clinical studies by analysis of reported retinal adverse events and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH insulin treatment groups were similar for patients with type 1 and type 2 diabetes.

LANTUS was compared to NPH insulin in a 5-year randomized clinical trial that evaluated the progression of retinopathy as assessed with fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Scale (ETDRS). Patients had type 2 diabetes (mean age 55 yrs) with no (86%) or mild (14%) retinopathy at baseline. Mean baseline HbA1c was 8.4%. The primary outcome was progression by 3 or more steps on the ETDRS scale at study endpoint. Patients with pre-specified post-baseline eye procedures (pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy, local photocoagulation for new vessels, and vitrectomy for diabetic retinopathy) were also considered as 3-step progressors regardless of actual change in ETDRS score from baseline. Retinopathy graders were blinded to treatment group assignment. The results for the primary endpoint are shown in Table 7 for both the per-protocol and Intent-to-Treat populations, and indicate similarity of Lantus to NPH in the progression of diabetic retinopathy as assessed by this outcome.

Oral antibiotics are an example, such as anti-inflammatory dose doxycycline (acne is an off-label indication).

This agent does not kill *Propionibacterium acnes*, but it can improve acne through an anti-inflammatory effect that is similar to full-dose doxycycline, Dr. Baldwin said.

One caveat: If you prescribe an oral antibiotic, you may experience push-back from some patients, Dr. Baldwin said. "I have women who say that they get a yeast infection every time they get an antibiotic." Strategies include antibiotic treatment through a yeast infec-

tion; a simultaneous prescription to prevent yeast growth; and/or selection of an antibiotic less likely to cause this effect. For example, extended-release minocycline may be less likely to spur yeast growth than traditional minocycline, she said.

Nonantibiotic alternatives for moderate to severe acne are limited, especially in women of child-bearing potential.

Oral hormonal contraceptives also can improve acne in adult women, Dr. Baldwin said. In the United States, ethinyl estradiol/norethindrone acetate (Estrostep, Warner Chilcott); drospir-

enone/ethinyl estradiol (Yaz, Bayer); and ethinyl estradiol/norgestimate (Ortho Tri-Cyclen, Ortho McNeil Janssen) are FDA-approved for acne treatment "and others with estrogen may be effective."

Because their full acne-fighting effects can take up to 6 months, Dr. Baldwin recommended prescription of oral contraceptives in combination with a quicker onset agent. "For me it's a medication on top of a medication that is going to give more immediate improvement, one I can take them off when I start to see the oral contraceptive kick in."

"The difference becomes significant with Yaz at about 6 months," Dr. Baldwin said. "But waiting for 6 months for this to happen is not something most of our patients will do."

Keep potential adverse effects of oral contraceptives in mind. Evidence in the literatures suggests there is no increased cardiovascular risk among non-smokers, Dr. Baldwin said.

In addition, studies indicate no increase risk of breast cancer. An increased likelihood for a thrombotic event is elevated during the first year then becomes normalized, she said.

The FDA added a black box warning to labeling for spironolactone (Aldactone, GD Searle, plus generics) in 2008 that cites an increased risk for tumors

Table 7. Number (%) of patients with 3 or more step progression on ETRS scale at endpoint

	Lantus (%)	NPH (%)	Difference ^{a,†} (SE)	95% CI for difference
Per-protocol	53/374 (14.2%)	57/363 (15.7%)	-2.0% (2.6%)	-7.0% to +3.1%
Intent-to-Treat	63/502 (12.5%)	71/487 (14.6%)	- 2.1% (2.1%)	-6.3% to +2.1%

^aDifference = Lantus - NPH

[†]Using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata (cutoff 9.0%) as the classified independent variables, and with binomial distribution and identity link function

• **Insulin initiation and intensification of glucose control**

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

• **Lipodystrophy**

Long-term use of insulin, including LANTUS, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. [See *Dosage and Administration (2.1)*].

• **Weight gain**

Weight gain can occur with insulin therapy, including LANTUS, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

• **Peripheral Edema**

Insulin, including LANTUS, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

• **Allergic Reactions**

Local Allergy

As with any insulin therapy, patients taking LANTUS may experience injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation. In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

Systemic Allergy

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LANTUS and may be life threatening.

• **Antibody production**

All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LANTUS, increases in titers of antibodies to insulin were observed in NPH insulin and insulin glargine treatment groups with similar incidences.

6.2 Postmarketing experience

The following adverse reactions have been identified during post-approval use of LANTUS.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of LANTUS [See *Patient Counseling Information (17)* in the full prescribing information]. To avoid medication errors between LANTUS and other insulins, patients should be instructed to always verify the insulin label before each injection.

7. DRUG INTERACTIONS

A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of drugs that may increase the blood-glucose-lowering effect of insulins including LANTUS and, therefore, increase the susceptibility to hypoglycemia: oral anti-diabetic products, pramlintide, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of drugs that may reduce the blood-glucose-lowering effect of insulins including LANTUS: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, iso-

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niazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m². In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m², were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of LANTUS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

8.3 Nursing Mothers

It is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when LANTUS is administered to a nursing woman. Use of LANTUS is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The safety and effectiveness of subcutaneous injections of LANTUS have been established in pediatric patients (age 6 to 15 years) with type 1 diabetes [see *Clinical Studies (14)* in the full prescribing information]. LANTUS has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes. LANTUS has not been studied in pediatric patients with type 2 diabetes.

Based on the results of a study in pediatric patients, the dose recommendation when switching to LANTUS is the same as that described for adults [see *Dosage and Administration (2.3)* and *Clinical Studies (14)* in the full prescribing information]. As in adults, the dosage of LANTUS must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

8.5 Geriatric Use

In controlled clinical studies comparing LANTUS to NPH insulin, 593 of 3890 patients (15%) with type 1 and type 2 diabetes were ≥65 years of age and 80 (2%) patients were ≥75 years of age. The only difference in safety or effectiveness in the subpopulation of patients ≥65 years of age compared to the entire study population was a higher incidence of cardiovascular events typically seen in an older population in both LANTUS and NPH insulin-treated patients.

Nevertheless, caution should be exercised when LANTUS is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly [See *Warnings and Precautions (5.3)*].

10. OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

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'I have women who say that they get a yeast infection every time they get an antibiotic.'

DR. BALDWIN

based on animal studies. The warning recommends use only for approved indications, "which acne is not," Dr. Baldwin explained.

There have been five cases of breast cancer reported in women taking spironolactone and other medications, but there was "no clear link to the medication." Also, a review article found no evidence of risk (J. Clin. Aesthet. Dermatol. 2009;2:16-22). Still you "need to discuss this risk with your patients," Dr. Baldwin said.

"A recent Cochrane review [Cochrane Database Syst. Rev. 2009;(2):CD000194] on spironolactone which concluded that, although it was very helpful for hirsutism and for alopecia, that it had no evidence-based medicine to support its use in the treatment of acne," Dr. Baldwin remarked in an interview.

"Now that flies in the face of numerous small studies which have demonstrated clearly over the years that spironolactone in doses from 50 to 200 mg per day are very helpful in the treatment of acne, especially in the adult woman," she added.

The number of participants in these studies was "so small that it didn't pass muster for the Cochrane review," Dr. Baldwin said. "I still believe spironolactone is an incredibly useful drug in the treatment of acne."

An estimated 13%-15% of women in the United States have acne. The number has been increasing in recent past.

Dr. Baldwin said, however, it is unclear if the increase is due to greater awareness of quality acne therapy and/or a true increase in prevalence. She recommended www.acneandrosacea.org for more information.

Dr. Baldwin is a consultant and has received honoraria from Ortho, Galderma, Allergan, Coria, Graceway, GlaxoSmithKline, and L'Oreal. SDEF and this news organization are owned by Elsevier. ■